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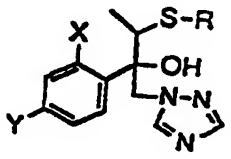
(54) Title: TRIAZOLE COMPOUNDS AND PROCESSES FOR THE PREPARATION THEREOF

(57) Abstract

Novel triazole compounds of formula (I), and pharmacologically acceptable salts thereof, possess potent antifungal activities, and are useful for the treatment of fungal infections.



(I)

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TRIAZOLE COMPOUNDS AND PROCESSES FOR THE PREPARATION THEREOF

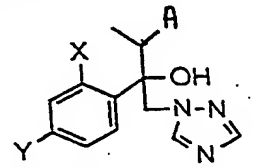
Field of the Invention

The present invention relates to novel triazole compounds with an antifungal activity, processes for the preparation of these compounds, and pharmaceutical compositions containing same as active ingredients.

Description of the Prior Art

Hitherto many studies have been made to develop various compounds having an antifungal activity for the treatment of fungal infections in mammals including human beings. Recently, triazole derivatives with a low toxicity for an oral administration, such as Fluconazole (GB 2099818) and Itraconazole (USP 4,276,179), have been reported.

As a known antifungal agent, triazole derivatives of the following formula have been published in EP 0322800 A1 and EP 0178533:



wherein A represents an alkyl substituted sulfone ($-SO_2-$), sulfoxy (-SO-) or sulfide (-S-) group,

Further, EP Nos. 47338 and 100193 disclose the compounds of the above formula wherein A represents a substituted methylthio group ($-S-CH_2-$). Similarly, a compound wherein A is a disulfide group($-S-SO_n-$) and a compound wherein A represents -S-C- or $-S-SO_n-$ group are provided in JP 3-258764 and EP 0421210, respectively. Also disclosed is a compound having a substituted thio group (EP 0061835, EP 0095828 and EP 0552974) or a dithiocarbamate group (EP 0446877) as the group A. However, there has continued to exist a need to develop more effective compounds with a superior antifungal activity and a lower toxicity.

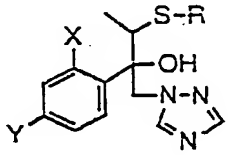
Summary of the Invention

Accordingly, it is a primary object of the present invention to provide novel triazole compounds having an excellent antifungal activity.

It is another object of the present invention to provide pharmaceutical compositions containing the same.

It is a further object of the present invention to provide processes for the preparation of said novel compounds.

In accordance with one aspect of the present invention, there are provided novel triazole compound of formula (I) and pharmacologically acceptable salts thereof:

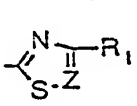


(I)

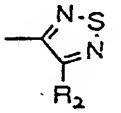
wherein,

X and Y are independently a hydrogen or halogen; and

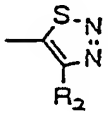
R is a group selected from the formulae consisting of (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g), (I-h), (I-i) and (I-j):



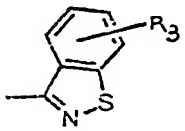
(I-a)



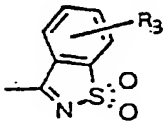
(I-b)



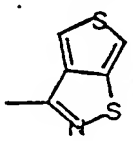
(I-c)



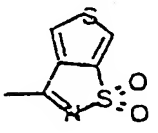
(I-d)



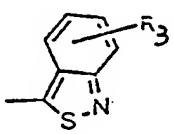
(I-e)



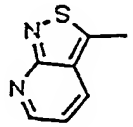
(I-f)



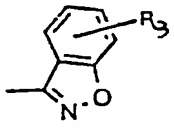
(I-g)



(I-h)



(I-i)



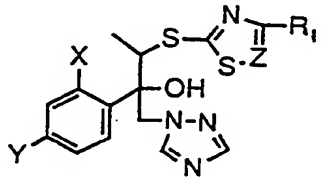
(I-j)

wherein Z is a nitrogen or carbon; R^1 represents a C_{1-4} alkoxy, C_{1-4} alkoxymethyl, C_{1-4} alkylthio, C_{1-4} alkylthiomethyl, amino, C_{1-4} alkylamino group which may form a ring with a nitrogen atom, or an optionally substituted C_{1-4} alkyl, styryl, phenyl or heteroaryl group; R^2 represents a hydrogen or a C_{1-3} alkyl, phenyl, substituted phenyl, morpholinyl, pyrrolidinyl, thiomorpholinyl or piperidinyl group; and R^3 represents a hydrogen or halogen or a C_{1-3} alkyl, C_{1-3} alkoxy or nitro group.

Detailed Description of the Invention

The triazole compounds of formula (I) of the present invention are characterized by a pentagonal or fused heterocyclic ring coupled to a sulfur atom as a substituent in 3-position.

Among the compounds of formula (I), preferred are the compounds of the following formula (I-A)



(I-A)

wherein X, Y, Z and R^1 are the same as defined in formula(I).

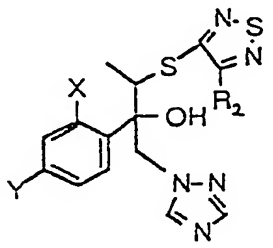
The compounds of formula (I-A) wherein Z is a nitrogen are those of formula (I) wherein R is a 1,2,4-thiadiazol group, and the compounds of formula (I-A) wherein Z is a carbon are those of formula (I) wherein R is a thiazol group.

Representative compounds thereof are shown in Table 1 below.

Table 1

Comp.	X	Y	Z	R_1
Ex. 3	F	F	N	cyclopropyl
Ex. 4	F	F	N	isopropyl
Ex. 5	F	F	N	methoxy
Ex. 6	F	F	N	chloromethyl
Ex. 7	F	F	N	dimethylamino
Ex. 9	F	F	N	amino
Ex.10	F	F	N	ethoxy
Ex.13	F	F	N	ethyl
Ex.19	F	F	N	4-fluorostyryl
Ex.20	F	F	N	4-(2,2,3,3-tetrafluoropropoxy)styryl
Ex.21	F	F	N	fluoromethyl
Ex.22	F	F	N	phenoxymethyl
Ex.34	F	F	N	4-chlorophenyl
Ex.41	F	F	N	2-pyrazinyl
Ex.47	F	F	N	styryl
Ex.55	F	F	N	pyrimidin-5-yl
Ex.57	F	F	N	4-(2,2,3,3-tetrafluoropropoxy)phenyl
Ex.60	F	F	N	pyridin-N-oxo-4-yl
Ex.63	F	F	N	3-nitrophenyl
Ex.64	F	F	N	2,5-difluorophenyl
Ex.69	F	F	N	pyrazin-3-yl
Ex.70	F	F	N	2-methoxy-1-chloromethyl
Ex.71	F	F	N	methoxymethyl
Ex.72	F	F	N	styryl(enantiomer)
Ex.73	F	F	N	methoxy(enantiomer)
Ex.77	F	F	C	2,4-difluorophenyl
Ex.80	F	F	C	ethyl
Ex.83	F	F	C	4-methoxystyryl
Ex.84	F	F	C	2,3-dichlorostyryl

Among the compounds of formula(I), also preferred compounds are the compounds (I) wherein R is a 1,2,5-thiadiazol group, i.e., the compounds having the following formula(I-B):



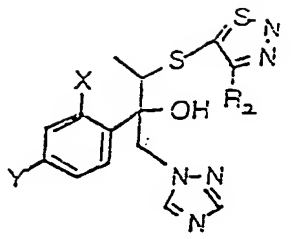
(I-B)

wherein X, Y and R_2 are the same as defined in formula(I). Representative compounds thereof are shown in Table 2 below.

Table 2

Compound	X	Y	R_2
Ex. 85	F	F	H
Ex. 86	H	Cl	H
Ex. 87	Cl	Cl	H
Ex. 88	F	F	methyl
Ex. 89	F	F	phenyl
Ex. 90	F	F	2,4-difluorophenyl (oxalate)
Ex. 91	F	F	H (oxalate)

Similarly preferred compounds of the present invention are those of formula(I) wherein R is a 1,2,3-thiadiazol group, i.e., the compounds having the following formula(I-C):



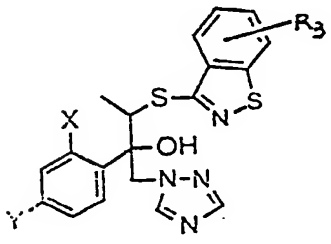
(I-C)

wherein X, Y and R_2 are the same as defined in formula(I). Representative compounds thereof are shown in Table 3 below.

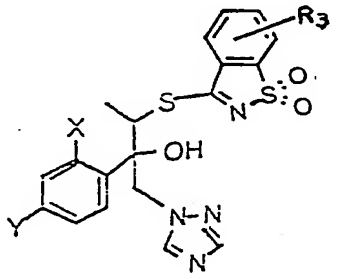
Table 3

Compound	X	Y	R_2
Ex. 92	H	F	N-morpholinyl
Ex. 93	F	F	N-thiomorpholinyl
Ex. 94	F	F	piperidin-1-yl (HCl)
Ex. 95	F	F	Pyrrolidin-1-yl
Ex. 96	F	F	N-thiomorpholinyl(enantiomer)

Further, the triazole compounds of the present invention include those of formula(I) wherein R is a fused heterocyclic ring selected from (I-d) to (I-j), i.e., the compounds having the following formulae (I-D) to (I-J):



(I-D)



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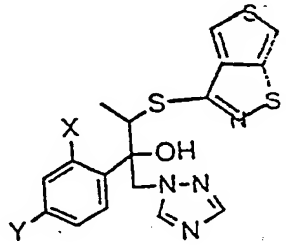
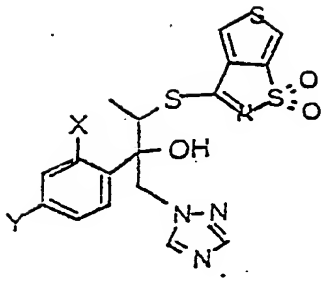


(I-F)



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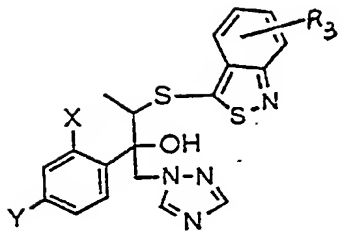
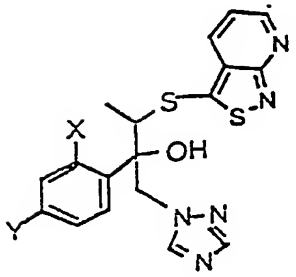
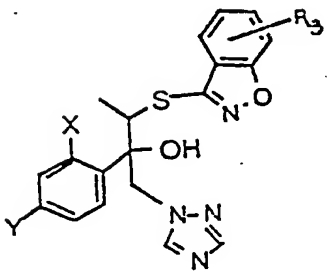


(I-H)



(I-I)



(I-J)

wherein X, Y and R_3 are the same as defined in formula(I). Representative compounds thereof are shown in Table 4 below.

Table 4

Comp.	X	Y	R_3
Ex.97	F	F	1,2-benzoisothiazol-3-yl
Ex.98	F	F	1,2-benzoisothiazol-3-yl (enantiomer)
Ex.99	H	Cl	1,2-benzoisothiazol-3-yl
Ex.100	H	F	1,2-benzoisothiazol-3-yl
Ex.101	F	F	5-chloro-1,2-benzoisothiazol-3-yl
Ex.102	H	Cl	5-chloro-1,2-benzoisothiazol-3-yl
Ex.103	F	F	5,6-dimethoxy-1,2-benzoisothiazol-3-yl
Ex.104	F	F	5-methyl-1,2-benzoisothiazol-3-yl
Ex.105	F	F	7-chloro-1,2-benzoisothiazol-3-yl
Ex.106	F	F	thieno[3,4-d]isothiazol-3-yl
Ex.107	F	F	1,2-benzoisothiazol-1,1-dioxo-3-yl
Ex.108	F	F	thieno[3,4-d]isothiazol-1,1-dioxo-3-yl
Ex.109	F	F	2,1-benzoisothiazol-3-yl
Ex.110	F	F	5-nitro-2,1-benzoisothiazol-3-yl
Ex.111	F	F	isothiazolo[3,4-d]pyridin-3-yl
Ex.112	F	F	1,2-benzoisothiazol-3-yl
Ex.113	F	F	thieno[3,4-d]isothiazol-3-yl (enantiomer)

The triazole compounds of formula(I) of the present invention include two asymmetric carbons in 2 and 3 positions; and, therefore, the present invention encompasses, within its scope, racemic mixtures of ($2R^*,3R^*$) form and an enantiomer of (2R,3R) form, as well as each diastereomers, which can be collectively represented by the formula (I).

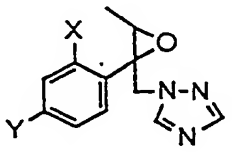
Furthermore, the present invention embraces, within its scope, those pharmacologically acceptable salts of the compounds of formula(I). Suitable pharmacologically acceptable salts of the triazole compounds(I) may include salts of inorganic and organic acids, such as hydrochloride,

nitrate, oxalate and methanesulfonate; and, in addition, other salts known in the art. Such pharmacologically acceptable salts of the compounds of formula(I) may be prepared by a conventional method.

The triazole compounds(I) of the present invention may be prepared in accordance with the following methods.

Method A

The triazole compounds of formula(I) of the present invention may be prepared by reacting a compound of formula(II) with a compound of formula(III) or its an alkali metal salt in the presence of lithium perchlorate ($LiClO_4$).



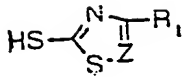
+ R - SH $\xrightarrow{LiClO_4}$ (I)

(II) (III)

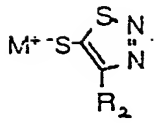
wherein X, Y and R are the same as defined previously.

The compound of formula(II) used in the present invention may be prepared, e.g., in accordance with the procedures described in EP Patent No. 421210.

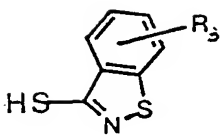
Further, the compound of formula(III) may be prepared by methods disclosed in various references, e.g., in accordance with the procedures described in Adv. Heterocycl. Chem., 5, 119 (1965) for the compound of formula(III-a); J. Heterocycl. Chem., 15, 1295 (1978) for the compound of formula(III-c); and Adv. Heterocycl. Chem., 14, 43 (1972) and J. Org. Chem., 47, 5255 (1982) for the compounds of formulae (III-d) to (III-j); or, alternatively, by reacting a corresponding isothiazol-3-thione derivatives with a thiol.



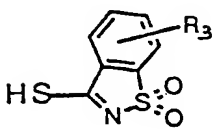
(III-a)



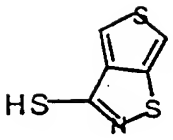
(III-c)



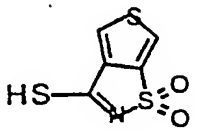
(III-d)



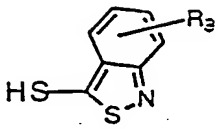
(III-e)



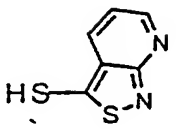
(III-f)



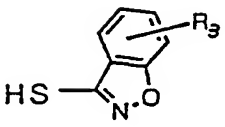
(III-g)



(III-h)



(III-i)



(III-j)

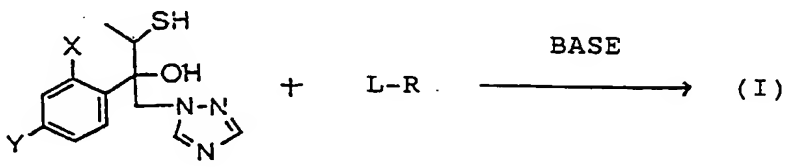
wherein R_1, R_2 and R_3 are the same as defined previously and M represents an alkali metal.

In the above method, the compound(II), the compound(III) and $LiClO_4$ are preferably employed in a molar ratio of 1 : 1 to 5 : 1 to 5, more preferably 1 : 1 to 2 : 1 to 2.

The above reaction may be conducted in an organic polar solvent such as methanol, acetonitrile, dimethylformamide and the like, at a temperature ranging from 50 to 130 °C, preferably from 80 to 110 °C, for a period ranging from 4 to 18 hours, preferably from 4 to 10 hours.

Method B

Alternatively, the triazole compounds of formula(I) of the present invention may be prepared by reacting a compound of formula(IV) with a compound of formula(V) in the presence of a base.

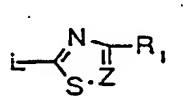


(IV) (V)

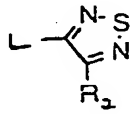
wherein X, Y and R are the same as defined previously, and L represents a halogen.

The compound of formula(IV) may be prepared, e.g., in accordance with the procedures described in EP Patent No. 421210.

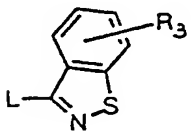
Further, the compound of formula(V) may be prepared by methods disclosed in various references, e.g., in accordance with the procedures described in Adv. Heterocycl. Chem., 5, 119 (1965) for the compound of formula (V-a); and Adv. Heterocycl. Chem., 14, 43 (1972), J. Org. Chem., 45, 617 (1980), Aust. J. Chem., 24, 2405 (1971), Can. J. Chem., 51, 1741 (1973), and Chem. Ber., 100, 3326 (1967) for the compounds of formulae (V-d) to (V-j); and by a replacement reaction of a corresponding 3,4-dichloro-1,2,5-thiadiazole derivatives, for the compound of formula(V-b).



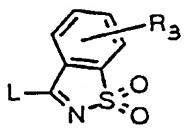
(V-a)



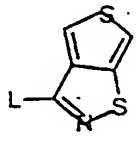
(V-b)



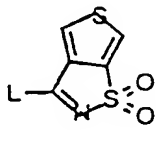
(V-d)



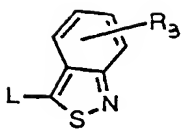
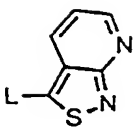
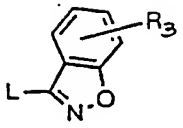
(V-e)



(V-f)



(V-g)

(V-h) (V-i) (V-j)

wherein R_1, R_2, R_3 and L are the same as defined previously.

The base which may be used in the above reaction includes an inorganic base such as sodium hydride (NaH), potassium carbonate (K_2CO_3) or sodium methoxide (MeONa), and an organic base such as triethylamine or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

The above reaction may be conducted in an organic polar solvent such as methanol, acetonitrile, dimethoxyethane, dimethylformamide and the like, at a temperature ranging from 0 to 25 °C, preferably from 0 to 5 °C, for a period ranging from 15 minutes to 2 hours, preferably from 15 to 30 minutes.

The present invention also provides pharmaceutical compositions containing the compounds of formula(I) and pharmacologically acceptable salts thereof as active ingredients, in association with pharmaceutically acceptable carriers, excipients or other additives, if necessary.

The pharmaceutical compositions of the present invention may be administered orally or by injection. The pharmaceutical composition for oral administration may take various forms such as tablets, granules, solutions and gelatin capsules, which may contain conventional additives such as a diluent, lubricant, absorbent, colorant, favour, sweetener and the like. The composition for injection may be an isotonic solution or a suspension, and may be sterilized and/or contain an adjuvant such as a preservative, stabilizer, wetting agent, emulsifier, a salt for controlling an osmotic pressure and/or a buffer solution, and other pharmaceutically effective materials.

The pharmaceutical composition may be administered for the treatment of fungal infections in a dosage ranging from

0.05 to 10 mg/kg/day, more preferably from 1.0 to 5 mg/kg/day, depending on the routes and frequency of administration, although the dosage may vary in accordance with the kind and severity of the disease.

The following Examples are given for the purpose of illustration only and are not intended to limit the scope of the invention.

Example 1 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-(3-t-butyl-1,2,4-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

A mixture of 0.502 g (0.002 mol) of (2R*, 3S*)-2-(2,4-difluorophenyl)-3-methyl-2-[(1H-1,2,4-triazol-1-yl)methyl]oxirane, 0.523 g (0.003 mol) of 3-t-butyl-1,2,4-thiadiazol-5-thiol and 0.319 g (0.003 mol) of lithium perchlorate in 6 ml of acetonitrile was stirred at 90 ± 3 °C for 10 hours. The reaction mixture was diluted with 100 ml of ethyl acetate, and washed with 5% sodium hydroxide aqueous solution (30 ml x 2) and then saline (30 ml x 1). The organic layer was dried over anhydrous magnesium sulfate and evaporated under reduced pressure to give a residue, which was purified by silica gel column chromatography and recrystallized from isopropyl ether/n-hexane to afford the title compound.

M.p. : 138 to 141 °C

^{1}H-NMR($CDCl_3$, δ, ppm) 1.30(d, 3H), 1.43(s, 9H), 4.50(q, 1H), 4.84 and 5.05(dd, 2H), 6.27(s, 1H), 6.74-7.47(m, 3H), 7.71 and 7.88(ss, 2H)

Example 2 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-(3-methylthio-1,2,4-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 1 above were repeated using 0.502 g (0.002 mol) of (2R*, 3S*)-2-(2,4-difluorophenyl)-3-methyl-2-[(1H-1,2,4-triazol-1-yl)methyl]oxirane and 0.523 g (0.003 mol) of 3-methylthio-

1,2,4-thiadiazol-5-thiol to afford the title compound.
M.p. : 149 to 154 °C
^{1}H-NMR(DMSO-d_6, δ, ppm) 1.24(d, 3H), 2.65(s, 3H), 4.57(q, 1H), 4.79(s, 2H), 6.62(s, 1H), 6.98-7.27(m, 3H), 7.67 and 8.21(ss, 2H)

Example 3 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-(3-cyclopropyl-1,2,4-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

A mixture of 0.571 g (0.002 mol) of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-mercapto-1-(1H-1,2,4-triazol-1-yl)-2-butanol, 0.48 g (0.003 mol) of 5-chloro-3-cyclopropyl-1,2,4-thiadiazole and 1.012 g (0.010 mol) of triethylamine in 6 ml of acetonitrile was stirred at 20 ± 2 °C for 30 minutes. The reaction mixture was evaporated under reduced pressure, diluted with 100 ml of ethyl acetate, and washed with 5% sodium hydroxide aqueous solution (30 ml x 2) and then saline (30 ml x 1). The organic layer was dried over anhydrous magnesium sulfate and evaporated under reduced pressure to give a residue, which was purified by silica gel column chromatography to afford the title compound.
M.p. : 159 to 161 °C
^{1}H-NMR($CDCl_3$, δ, ppm) 1.13-1.32(m, 4H), 1.26(d, 3H), 2.35(s, 1H), 4.51(q, 1H), 4.88 and 5.00(dd, 2H), 6.18(s, 1H), 6.77-7.50(m, 3H), 7.77 and 8.88(ss, 2H)

Example 4 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-(3-isopropyl-1,2,4-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 3 above were repeated using 0.488 g (0.003 mol) of 5-chloro-3-isopropyl-1,2,4-thiadiazole in place of 5-chloro-3-cyclopropyl-1,2,4-thiadiazole to afford the title compound.
M.p. : 147 to 149 °C
^{1}H-NMR($CDCl_3$, δ, ppm) 1.26-1.42(m, 9H), 3.32(m, 1H), 4.53(q, 1H), 4.90 and 5.05(dd, 2H), 6.75-7.50(m, 3H), 7.77 and

7.90(ss, 2H)

Example 5 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-(3-methoxy-1,2,4-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 3 above were repeated using 0.452 g (0.003 mol) of 5-chloro-3-methoxy-1,2,4-thiadiazole in place of 5-chloro-3-cyclopropyl-1,2,4-thiadiazole to afford the title compound.
M.p. : 155 to 158 °C
^{1}H-NMR($CDCl_3$, δ, ppm) 1.29(d, 3H), 4.11(s, 3H), 4.61(q, 1H), 4.90 and 5.02(dd, 2H), 6.70-7.50(m, 3H), 7.77 and 7.83(ss, 2H)

Example 6 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-(3-chloromethyl-1,2,4-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 3 above were repeated using 0.507 g (0.003 mol) of 5-chloro-3-chloromethyl-1,2,4-thiadiazole in place of 5-chloro-3-cyclopropyl-1,2,4-thiadiazole to afford the title compound.
M.p. : 110 to 113 °C
^{1}H-NMR($CDCl_3$, δ, ppm) 1.36(d, 3H), 4.78(q, 1H), 4.81(s, 2H), 4.92 and 5.12(dd, 2H), 6.85-7.60(m, 3H), 7.83 and 7.90(ss, 2H)

Example 7 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-(3-dimethylamino-1,2,4-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 3 above were repeated using 0.491 g (0.003 mol) of 5-chloro-3-dimethylamino-1,2,4-thiadiazole in place of 5-chloro-3-cyclopropyl-1,2,4-thiadiazole to afford the title compound.
M.p. : 120 to 123 °C
^{1}H-NMR($CDCl_3$, δ, ppm) 1.32(d, 3H), 3.22(d, 6H), 4.51(q, 1H),

4.93 and 5.03(dd, 2H), 6.00(s, 1H), 6.75-7.55(m, 3H), 7.76 and 7.88(ss, 2H)

Example 8 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(pyrrolidin-1-yl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol oxalate

The same procedures as in Example 3 above were repeated using 0.569 g (0.003 mol) of 5-chloro-3-(pyrrolidin-1-yl)-1,2,4-thiadiazole in place of 5-chloro-3-cyclopropyl-1,2,4-thiadiazole to afford the title compound.
M.p. : 91 to 95 °C
^{1}H-NMR(DMSO-d_6, δ, ppm) 1.19(d, 3H), 2.90(m, 4H), 3.49(m, 4H), 4.68(q, 1H), 4.77 and 4.93(dd, 2H), 6.80-7.30(m, 3H), 7.65 and 8.29(ss, 2H)

Example 9 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-(3-amino-1,2,4-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 3 above were repeated using 0.407 g (0.003 mol) of 5-chloro-3-amino-1,2,4-thiadiazole in place of 5-chloro-3-cyclopropyl-1,2,4-thiadiazole to afford the title compound.
M.p. : 130 to 132 °C
^{1}H-NMR($CDCl_3$, δ, ppm) 1.32(d, 3H), 4.50(q, 1H), 4.90-5.20(m, 4H), 5.14(s, 1H), 6.76-7.50(m, 3H), 7.81 and 7.97(ss, 2H)

Example 10 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-(3-ethoxy-1,2,4-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 3 above were repeated using 0.494 g (0.003 mol) of 5-chloro-3-ethoxy-1,2,4-thiadiazole in place of 5-chloro-3-cyclopropyl-1,2,4-thiadiazole to afford the title compound.
M.p. : 154 to 158 °C
^{1}H-NMR($CDCl_3$, δ, ppm) 1.27(d, 3H), 1.49(t, 3H), 4.49(q, 2H),

4.60(q, 1H), 4.95(dd, 2H), 5.64(s, 1H), 6.65-7.48(m, 3H), 7.79 and 7.83(ss, 2H)

Example 11 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-(3-methacryl-1,2,4-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 3 above were repeated using 0.482 g (0.003 mol) of 5-chloro-3-methacryl-1,2,4-thiadiazole in place of 5-chloro-3-cyclopropyl-1,2,4-thiadiazole to afford the title compound.
M.p. : 116 to 118 °C
^{1}H-NMR(DMSO-d_6, δ, ppm) 1.25(d, 3H), 2.18(s, 3H), 4.84(m, 3H), 5.65 and 6.27(d, 2H), 6.58(s, 1H), 7.00-7.29(m, 3H), 7.67 and 8.29(ss, 2H)

Example 12 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-(3-methylthiomethyl-1,2,4-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 3 above were repeated using 0.542 g (0.003 mol) of 5-chloro-3-methylthiomethyl-1,2,4-thiadiazole in place of 5-chloro-3-cyclopropyl-1,2,4-thiadiazole to afford the title compound.
M.p. : 129 to 132 °C
^{1}H-NMR(DMSO-d_6, δ, ppm) 1.25(d, 3H), 2.17(s, 3H), 3.92(s, 2H), 4.70(q, 1H), 4.82(dd, 2H), 6.62(s, 1H), 7.00-7.25(m, 3H), 7.68 and 8.28(ss, 2H)

Example 13 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-(3-ethyl-1,2,4-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 3 above were repeated using 0.446 g (0.003 mol) of 5-chloro-3-ethyl-1,2,4-thiadiazole in place of 5-chloro-3-cyclopropyl-1,2,4-thiadiazole to afford the title compound.
M.p. : 130 to 132 °C

^{1}H-NMR($CDCl_3$, δ, ppm) 1.34(d, 3H), 1.45(t, 3H), 3.02(q, 2H), 4.60(q, 1H), 5.00(dd, 2H), 6.10(s, 1H), 6.80-7.50(m, 3H), 7.78 and 7.91(ss, 2H)

Example 14 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(1-chloroethyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 3 above were repeated using 0.549 g (0.003 mol) of 5-chloro-3-(1-chloroethyl)-1,2,4-thiadiazole in place of 5-chloro-3-cyclopropyl-1,2,4-thiadiazole to afford the title compound.
M.p. : 140 to 143 °C
^{1}H-NMR($CDCl_3$, δ, ppm) 1.32(d, 3H), 2.00(s, 3H), 4.70(q, 2H), 4.85 and 5.08(dd, 2H), 5.27(m, 2H), 5.70(s, 1H), 6.74-7.45(m, 3H), 7.77 and 7.83(ss, 2H)

Example 15 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-(3-methoxymethyl-1,2,4-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 3 above were repeated using 0.494 g (0.003 mol) of 5-chloro-3-methoxymethyl-1,2,4-thiadiazole in place of 5-chloro-3-cyclopropyl-1,2,4-thiadiazole to afford the title compound.
M.p. : 73 to 76 °C
^{1}H-NMR($CDCl_3$, δ, ppm) 1.20(d, 3H), 3.50(q, 1H), 3.93(s, 2H), 4.22(s, 2H), 4.75 and 5.03(dd, 2H), 5.15(s, 1H), 6.69-7.45(m, 3H), 7.75 and 7.82(ss, 2H)

Example 16 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(4-methoxystyryl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 3 above were repeated using 0.758 g (0.003 mol) of 5-chloro-3-(4-methoxystyryl)-1,2,4-thiadiazole in place of 5-chloro-3-cyclopropyl-1,2,4-thiadiazole to afford the title compound.

M.p. : 129 to 131 °C
^{1}H-NMR($CDCl_3$, δ, ppm) 1.34(d, 3H), 3.86(s, 3H), 4.75(m, 3H), 5.01(dd, 2H), 5.85(s, 1H), 6.71-7.54(m, 7H), 7.07 and 7.79(dd, 2H), 7.78 and 7.82(ss, 2H)

Example 17 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(3,5-dimethylpyrazol-1-yl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 3 above were repeated using 0.644 g (0.003 mol) of 5-chloro-3-(3,5-dimethylpyrazol-1-yl)-1,2,4-thiadiazole in place of 5-chloro-3-cyclopropyl-1,2,4-thiadiazole to afford the title compound.
M.p. : 178 to 181 °C
^{1}H-NMR($CDCl_3$, δ, ppm) 1.35(d, 3H), 2.35 and 2.67(ss, 6H), 4.70 and 5.01(dd, 2H), 5.70(s, 1H), 6.06(s, 1H), 6.80-7.45(m, 3H), 7.79 and 7.91(ss, 2H)

Example 18 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-(3-crotyl-1,2,4-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 3 above were repeated using 0.482 g (0.003 mol) of 5-chloro-3-crotyl-1,2,4-thiadiazole in place of 5-chloro-3-cyclopropyl-1,2,4-thiadiazole to afford the title compound.
M.p. : 95 to 97 °C
^{1}H-NMR($CDCl_3$, δ, ppm) 1.32(d, 3H), 2.01(dd, 3Hx0.75), 2.18(dd, 3Hx0.25), 4.64(q, 1H), 4.97(dd, 2H), 5.78(brs, 1Hx0.25), 9.57(brs, 1Hx0.75), 6.17-6.35(m, 1Hx0.25), 6.60(d, 1H), 6.70-7.55(m, 3H), 7.77 and 7.87(ss, 2H)

Example 19 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(4-fluorostyryl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 3 above were repeated using 0.722 g (0.003 mol) of 5-chloro-3-(4-fluorostyryl)-

1,2,4-thiadiazole in place of 5-chloro-3-cyclopropyl-1,2,4-thiadiazole to afford the title compound.

M.p. : 167 to 169 °C

^{1}H-NMR($CDCl_3$, δ, ppm) 1.35(d, 3H), 4.76(q, 1H), 5.03(dd, 2H), 5.81(s, 1H), 6.73-7.65(m, 7H), 6.08-7.80(m, 2H), 7.79 and 7.86(ss, 2H)

Example 20 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(4-(2,2,3,3-tetrafluoropropoxy)styryl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 3 above were repeated using 1.058 g (0.003 mol) of 5-chloro-3-[4-(2,2,3,3-tetrafluoropropoxy)styryl]-1,2,4-thiadiazole in place of 5-chloro-3-cyclopropyl-1,2,4-thiadiazole to afford the title compound.

M.p. : 109 to 111 °C

^{1}H-NMR($CDCl_3$, δ, ppm) 1.35(d, 3H), 4.40(t, 2H), 4.74(q, 1H), 5.11(dd, 2H), 5.82(s, 1H), 5.52, 6.08 and 6.38(t, 1H), 6.73-7.59(m, 7H), 7.10 and 7.79(dd, 2H), 7.79 and 7.87(ss, 2H)

Example 21 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-(3-fluoromethyl-1,2,4-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 3 above were repeated using 0.458 g (0.003 mol) of 5-chloro-3-fluoromethyl-1,2,4-thiadiazole in place of 5-chloro-3-cyclopropyl-1,2,4-thiadiazole to afford the title compound.

M.p. : 106 to 108 °C

^{1}H-NMR($CDCl_3$, δ, ppm) 1.31(d, 3H), 4.68(q, 1H), 4.91 and 5.03(dd, 2H), 5.44 and 5.67(dd, 2H), 5.65(s, 1H), 6.78-7.50(m, 3H), 7.80 and 7.84(ss, 2H)

Example 22 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-(3-phenoxymethyl-1,2,4-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol HCl

The same procedures as in Example 3 above were repeated using 0.680 g (0.003 mol) of 5-chloro-3-phenoxymethyl-1,2,4-thiadiazole in place of 5-chloro-3-cyclopropyl-1,2,4-thiadiazole and then the resulting product was recrystallized from ethylether by the addition of 5 ml of HCl-saturated ethyl ether to afford the title compound.
M.p. : 143 to 146 °C
^{1}H-NMR(DMSO-d_6, δ, ppm) 1.25(d, 3H), 4.07(m, 2H), 4.87(s, 2H), 5.35(s, 2H), 6.60-7.40(m, 3H), 8.04 and 8.85(ss, 2H)

Example 23 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(2-fluorophenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 1 above were repeated using 0.637 g (0.003 mol) of 3-(2-fluorophenyl)-1,2,4-thiadiazol-5-thiol in place of 3-t-butyl-1,2,4-thiadiazol-5-thiol and then the resulting product was recrystallized from diethyl ether to afford the title compound.
M.p. : 133 to 136 °C
^{1}H-NMR(DMSO-d_6, δ, ppm) 1.00(d, 3H), 4.57(m, 3H), 6.34(s, 1H), 6.68-7.30(m, 7H), 7.37 and 7.99(ss, 2H)

Example 24 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(2,6-difluorophenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 1 above were repeated using 0.691 g (0.003 mol) of 3-(2,6-difluorophenyl)-1,2,4-thiadiazol-5-thiol in place of 3-t-butyl-1,2,4-thiadiazol-5-thiole to afford the title compound.
M.p. : 175 to 179 °C
^{1}H-NMR(DMSO-d_6, δ, ppm) 1.27(d, 3H), 4.85(m, 3H), 6.63(s, 1H), 6.90-7.70(m, 6H), 7.67 and 8.27(ss, 2H)

Example 25 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(4-fluorophenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 1 above were repeated using 0.637 g (0.003 mol) of 3-(4-fluorophenyl)-1,2,4-thiadiazol-5-thiol in place of 3-t-butyl-1,2,4-thiadiazol-5-thiol to afford the title compound.

M.p. : 133 to 138 °C

^{1}H-NMR(DMSO-d_6, δ, ppm) 1.30(d, 3H), 4.90(m, 3H), 6.65(s, 1H), 7.02-8.40(m, 7H), 7.70 and 8.25(ss, 2H)

Example 26 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(2-pyridyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 1 above were repeated using 0.586 g (0.003 mol) of 3-(2-pyridyl)-1,2,4-thiadiazol-5-thiol in place of 3-t-butyl-1,2,4-thiadiazol-5-thiol to afford the title compound.

M.p. : 174 to 176.5 °C

^{1}H-NMR($CDCl_3$, δ, ppm) 1.37(d, 3H), 4.75(q, 1H), 4.95 and 5.09(dd,2H), 5.90(s, 1H), 7.40-8.84(m, 7H), 7.77 and 7.91(ss, 2H)

Example 27 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(2-chlorophenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 1 above were repeated using 0.686 g (0.003 mol) of 3-(2-chlorophenyl)-1,2,4-thiadiazol-5-thiol in place of 3-t-butyl-1,2,4-thiadiazol-5-thiol to afford the title compound.

M.p. : 125 to 127.5 °C

^{1}H-NMR(DMSO-d_6, δ, ppm) 1.20(d, 3H), 4.88(m, 3H), 6.65(s, 1H), 7.00-7.90(m, 6H), 7.70 and 8.30(ss, 2H)

Example 28 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-(3-phenyl-1,2,4-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 1 above were repeated using 0.583 g (0.003 mol) of 3-phenyl-1,2,4-thiadiazol-5-thiol in place of 3-t-butyl-1,2,4-thiadiazol-5-thiol to afford the title compound.

M.p. : 135 to 138 °C

^{1}H-NMR(DMSO-d_6, δ, ppm) 1.31(d, 3H), 4.82(m, 3H), 6.63(s, 1H), 7.02-8.21(m, 8H), 7.68 and 8.29(ss, 2H)

Example 29 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(3-pyridyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 1 above were repeated using 0.586 g (0.003 mol) of 3-(3-pyridyl)-1,2,4-thiadiazol-5-thiol in place of 3-t-butyl-1,2,4-thiadiazol-5-thiol to afford the title compound.

M.p. : 146 to 149 °C

^{1}H-NMR($CDCl_3$, δ, ppm) 1.36(d, 3H), 4.90(m, 1H), 4.95 and 5.11(dd, 2H), 5.66(s, 1H), 6.78-9.56(m, 6H), 7.80 and 7.81(ss, 2H)

Example 30 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(4-pyridyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 1 above were repeated using 0.586 g (0.003 mol) of 3-(4-pyridyl)-1,2,4-thiadiazol-5-thiol in place of 3-t-butyl-1,2,4-thiadiazol-5-thiol to afford the title compound.

M.p. : 178 to 180 °C

^{1}H-NMR($CDCl_3$, δ, ppm) 1.37(d, 3H), 4.90(m, 1H), 4.95 and 5.09(dd, 2H), 5.66(s, 1H), 6.80-7.46(m, 3H), 7.81 and 7.81(ss, 2H), 8.13-8.80(m, 4H)

Example 31 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[4-(1-(N-hydroxyiminoethyl)phenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 1 above were repeated using 0.754 g (0.003 mol) of 4-(1-(N-hydroxyiminoethyl) phenyl)-1,2,4-thiadiazol-5-thiol in place of 3-t-butyl-1,2,4-thiadiazol-5-thiol to afford the title compound.

M.p. : 177 to 180 °C

^{1}H-NMR($CDCl_3$, δ, ppm) 1.37(d, 3H), 4.88(m, 1H), 4.96 and 5.12(dd, 2H), 5.84(s, 1H), 6.80-7.87(m, 7H), 8.30 and 8.37(ss, 2H), 9.33(s, 1H)

Example 32 : Synthesis of (2R*, 3R*)-2-(4-chlorophenyl)-3-[3-(3,5-difluorophenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 1 above were repeated using 0.499 g (0.002 mol) of (2R*, 3S*)-2-(4-chlorophenyl)-3-methyl-2-[(1H-1,2,4-triazol-1-yl)methyl]oxirane and 0.691 g (0.003 mol) of 3-(3,5-difluorophenyl)-1,2,4-thiadiazol-5-thiol in place of (2R*, 3S*)-2-(2,4-difluorophenyl)-3-methyl-2-[(1H-1,2,4-triazol-1-yl)methyl]oxirane and 3-t-butyl-1,2,4-thiadiazol-5-thiol, respectively, to afford the title compound.

M.p. : 104 to 106 °C

^{1}H-NMR(DMSO-d_6, δ, ppm) 1.34(d, 3H), 4.50(m, 1H), 4.90(dd, 2H), 6.44(s, 1H), 7.44-7.85(m, 6H), 7.87 and 8.24(ss, 2H)

Example 33 : Synthesis of (2R*, 3R*)-2-(2,4-dichlorophenyl)-3-[3-(4-pyridyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 1 above were repeated using 0.499 g (0.002 mol) of (2R*, 3S*)-2-(2,4-dichlorophenyl)-3-methyl-2-[(1H-1,2,4-triazol-1-yl)methyl]oxirane and 0.586 g (0.003 mol) of 3-(4-pyridyl)-1,2,4-thiadiazol-5-thiol in place of (2R*, 3S*)-2-(2,4-difluorophenyl)-3-methyl-2-[(1H-1,2,4-triazol-1-yl)methyl]oxirane and 3-t-butyl-1,2,4-thiadiazol-5-thiol, respectively, to afford the title compound.

M.p. : 142 to 144 °C

^{1}H-NMR($CDCl_3$, δ, ppm) 1.32(d, 3H), 4.90 and 5.63(dd, 2H), 5.45(q, 1H), 5.70(s, 1H), 7.15-7.60(m, 3H), 7.81(s, 2H), 8.15-8.18(m, 4H)

Example 34 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(4-chlorophenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 1 above were repeated using 0.686 g (0.003 mol) of 3-(4-chlorophenyl)-1,2,4-thiadiazol-5-thiol in place of 3-t-butyl-1,2,4-thiadiazol-5-thiol to afford the title compound.

M.p. : 156 to 159 °C

^{1}H-NMR(DMSO-d_6, δ, ppm) 1.30(d, 3H), 4.85(m, 3H), 6.64(s, 1H), 6.95-8.23(m, 7H), 7.68 and 8.27(ss, 2H)

Example 35 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(3-fluorophenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 1 above were repeated using 0.637 g (0.003 mol) of 3-(3-fluorophenyl)-1,2,4-thiadiazol-5-thiol in place of 3-t-butyl-1,2,4-thiadiazol-5-thiol to afford the title compound.

M.p. : 123 to 125 °C

^{1}H-NMR($CDCl_3$, δ, ppm) 1.36(d, 3H), 4.88(m, 1H), 5.10(dd, 1H), 5.68(s, 1H), 6.70-8.20(m, 7H), 7.79 and 7.82(ss, 2H)

Example 36 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(3,4-difluorophenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 1 above were repeated using 0.691 g (0.003 mol) of 3-(3,4-difluorophenyl)-1,2,4-thiadiazol-5-thiol in place of 3-t-butyl-1,2,4-thiadiazol-5-thiol to afford the title compound.

M.p. : 137 to 139.5 °C

^{1}H-NMR($CDCl_3$, δ, ppm) 1.35(d, 3H), 4.88(q, 1H), 5.01(dd, 2H),

5.65(s, 1H), 6.70-8.20(m, 6H), 7.80(s, 2H)

Example 37 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(2,6-dichlorophenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 1 above were repeated using 0.790 g (0.003 mol) of 3-(2,6-dichlophenyl)-1,2,4-thiadiazol-5-thiol in place of 3-t-butyl-1,2,4-thiadiazol-5-thiol to afford the title compound.
M.p. : 138 to 140 °C
^{1}H-NMR($CDCl_3$, δ, ppm) 1.29(d, 3H), 4.85(m, 3H), 5.71(s, 1H), 6.95-7.80(m, 6H), 7.70 and 8.32(ss, 2H)

Example 38 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(3-trifluoromethylphenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 1 above were repeated using 0.787 g (0.003 mol) of 3-(3-trifluoromethylphenyl)-1,2,4-thiadiazol-5-thiol in place of 3-t-butyl-1,2,4-thiadiazol-5-thiol to afford the title compound.
M.p. : 144 to 146 °C
^{1}H-NMR($CDCl_3$, δ, ppm) 1.35(d, 3H), 4.90(q, 1H), 5.08(dd, 2H), 5.59(s, 1H), 6.70-8.65(m, 7H), 7.77 and 7.82(ss, 2H)

Example 39 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(3-chlorophenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 1 above were repeated using 0.686 g (0.003 mol) of 3-(3-chlorophenyl)-1,2,4-thiadiazol-5-thiol in place of 3-t-butyl-1,2,4-thiadiazol-5-thiol to afford the title compound.
M.p. : 118 to 120 °C
^{1}H-NMR($CDCl_3$, δ, ppm) 1.35(d, 3H), 4.87(q, 1H), 5.02(dd, 2H), 5.64(s, 1H), 6.72-8.32(m, 7H), 7.79 and 7.82(ss, 2H)

Example 40 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(4-(1H-imidazol-1-yl)phenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 1 above were repeated using 0.781 g (0.003 mol) of 3-(4-(1H-imidazol-1-yl)phenyl)-1,2,4-thiadiazol-5-thiol in place of 3-t-butyl-1,2,4-thiadiazol-5-thiol to afford the title compound.
M.p. : 227 to 230 °C
^{1}H-NMR($CDCl_3$, δ, ppm) 1.38(d, 3H), 4.90(m, 1H), 4.97 and 5.09(dd, 2H), 5.75(s, 1H), 6.80-7.83(m, 7H), 7.27 and 7.99(ss, 2H), 8.40 and 8.45(ss, 2H)

Example 41 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(2-pyrazinyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 1 above were repeated using 0.589 g (0.003 mol) of 3-(2-pyrazinyl)-1,2,4-thiadiazol-5-thiol in place of 3-t-butyl-1,2,4-thiadiazol-5-thiol to afford the title compound.
M.p. : 157 to 160 °C
^{1}H-NMR($CDCl_3$, δ, ppm) 1.36(d, 3H), 4.86(m, 3H), 4.95 and 5.10(dd, 2H), 5.72(s, 1H), 6.70-7.50(m, 3H), 7.80 and 8.83(ss, 2H), 8.73 and 9.60(m, 3H)

Example 42 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(2-chloro-6-fluorophenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 1 above were repeated using 0.740 g (0.003 mol) of 3-(2-chloro-6-fluorophenyl)-1,2,4-thiadiazol-5-thiol in place of 3-t-butyl-1,2,4-thiadiazol-5-thiol to afford the title compound.
M.p. : 117 to 119 °C
^{1}H-NMR($CDCl_3$, δ, ppm) 1.32(d, 3H), 4.70(q, 1H), 5.16(dd, 2H), 5.73(s, 1H), 6.67-7.55(m, 6H), 7.76 and 7.84(ss, 2H)

Example 43 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(4-bromophenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 1 above were repeated using 0.820 g (0.003 mol) of 3-(4-bromophenyl)-1,2,4-thiadiazol-5-thiol in place of 3-t-butyl-1,2,4-thiadiazol-5-thiol to afford the title compound.

M.p. : 163 to 165 °C

^{1}H-NMR(DMSO-d_6, δ, ppm) 1.29(d, 3H), 4.85(m, 3H), 6.64(s, 1H), 7.00-8.10(m, 7H), 7.68 and 8.28(ss, 2H)

Example 44 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(4-(1H-1,2,4-triazol-1-yl)phenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 1 above were repeated using 0.784 g (0.003 mol) of 3-(4-(1H-1,2,4-triazol-1-yl)phenyl)-1,2,4-thiadiazol-5-thiol in place of 3-t-butyl-1,2,4-thiadiazol-5-thiol to afford the title compound.

M.p. : 193 to 196 °C

^{1}H-NMR($CDCl_3$, δ, ppm) 1.38(d, 3H), 4.90(m, 1H), 4.96 and 5.10(dd, 2H), 5.70(s, 1H), 6.80-7.90(m, 7H), 8.17 and 8.43(ss, 2H), 8.47 and 8.69(ss, 2H)

Example 45 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(4-azidophenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 1 above were repeated using 0.706 g (0.003 mol) of 3-(4-azidophenyl)-1,2,4-thiadiazol-5-thiol in place of 3-t-butyl-1,2,4-thiadiazol-5-thiol to afford the title compound.

M.p. : 123 to 125 °C

^{1}H-NMR($CDCl_3$, δ, ppm) 1.35(d, 3H), 4.86(q, 1H), 4.94 and 5.08(dd, 2H), 5.77(s, 1H), 6.80-8.33(m, 7H), 7.78 and 7.83(ss, 2H)

Example 46 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(3,5-bistrifluoromethylphenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 1 above were repeated using 0.991 g (0.003 mol) of 3-(3,5-bistrifluoromethylphenyl)-1,2,4-thiadiazol-5-thiol in place of 3-t-butyl-1,2,4-thiadiazol-5-thiol to afford the title compound.

M.p. : 123 to 125 °C

^{1}H-NMR(DMSO-d_6, δ, ppm) 1.29(d, 3H), 4.90(m, 3H), 6.63(s, 1H), 7.00-8.40(m, 6H), 8.60 and 8.70(ss, 2H)

Example 47 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-(3-styryl-1,2,4-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 1 above were repeated using 0.661 g (0.003 mol) of 3-styryl-1,2,4-thiadiazol-5-thiol in place of 3-t-butyl-1,2,4-thiadiazol-5-thiol to afford the title compound.

M.p. : 151 to 153 °C

^{1}H-NMR($CDCl_3$, δ, ppm) 1.36(d, 3H), 4.68(q, 1H), 4.96 and 5.05(dd, 2H), 5.50(s, 1H), 6.78-7.63(m, 8H), 7.08 and 7.68(dd,2H), 7.82(ss, 2H)

Example 48 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(4-morpholin-1-yl)phenyl-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 1 above were repeated using 0.838 g (0.003 mol) of 3-(4-morpholin-1-yl)phenyl-1,2,4-thiadiazol-5-thiol in place of 3-t-butyl-1,2,4-thiadiazol-5-thiol to afford the title compound.

M.p. : 169 to 171 °C

^{1}H-NMR($CDCl_3$, δ, ppm) 1.35(d, 3H), 3.31 and 3.90(m, 8H), 4.75(q, 1H), 4.93 and 5.09(dd, 2H), 6.05(s, 1H), 6.79-8.02(m, 7H), 7.76 and 7.87(ss, 2H)

Example 49 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(3-trifluoromethyl-4-acetylamino)phenyl-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 1 above were repeated using 0.958 g (0.003 mol) of 3-(3-trifluoromethyl-4-acetylamino)phenyl-1,2,4-thiadiazol-5-thiol in place of 3-t-butyl-1,2,4-thiadiazol-5-thiol to afford the title compound.
M.p. : 123 to 125 °C
^{1}H-NMR(DMSO-d_6, δ, ppm) 1.29(d, 3H), 2.11(s, 3H), 4.88(m, 3H), 6.63(s, 1H), 7.00-8.40(m, 6H), 7.67 and 8.28(ss, 2H), 9.72(s, 1H)

Example 50 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(4-(1,3,4-oxadiazol-2-yl)phenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 1 above were repeated using 0.787 g (0.003 mol) of 3-(4-(1,3,4-oxadiazol-2-yl)phenyl)-1,2,4-thiadiazol-5-thiol in place of 3-t-butyl-1,2,4-thiadiazol-5-thiol to afford the title compound.
M.p. : 122 to 125 °C
^{1}H-NMR(DMSO-d_6, δ, ppm) 1.35(d, 3H), 4.90(m, 3H), 6.68(s, 1H), 7.00-8.42(m, 7H), 7.72 and 8.32(ss, 2H), 9.46(s, 1H)

Example 51 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(4-(1,3-dioxolan-2-yl)phenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 1 above were repeated using 0.799 g (0.003 mol) of 3-(4-(1,3-dioxolan-2-yl)phenyl)-1,2,4-thiadiazol-5-thiol in place of 3-t-butyl-1,2,4-thiadiazol-5-thiol to afford the title compound.
M.p. : 138 to 140 °C
^{1}H-NMR(DMSO-d_6, δ, ppm) 1.31(d, 3H), 4.04-4.14(m, 4H), 4.83(m, 1H), 4.89 and 5.06(dd, 2H), 5.74(s, 1H), 5.86(s, 1H), 6.70-8.30(m, 7H), 7.74 and 7.78(ss, 2H)

Example 52 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(4-cyanophenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 1 above were repeated using 0.658 g (0.003 mol) of 3-(4-cyanophenyl)-1,2,4-thiadiazol-5-thiol in place of 3-t-butyl-1,2,4-thiadiazol-5-thiol to afford the title compound.
M.p. : 195 to 197 °C
^{1}H-NMR($CDCl_3$, δ, ppm) 1.37(d, 3H), 4.88(q, 1H), 4.96 and 5.07(dd, 2H), 5.60(s, 1H), 6.75-8.44(m, 7H), 7.81 and 7.84(ss, 2H)

Example 53 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(thiophen-2-yl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 1 above were repeated using 0.601 g (0.003 mol) of 3-(thiophen-2-yl)-1,2,4-thiadiazol-5-thiol in place of 3-t-butyl-1,2,4-thiadiazol-5-thiol to afford the title compound.
M.p. : 122 to 125 °C
^{1}H-NMR(DMSO-d_6, δ, ppm) 1.28(d, 3H), 4.83(m, 3H), 6.60(s, 1H), 7.00-7.82(m, 6H), 7.67 and 8.29(ss, 2H)

Example 54 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(4-nitrophenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol oxalate

The same procedures as in Example 1 above were repeated using 0.718 g (0.003 mol) of 3-(4-nitrophenyl)-1,2,4-thiadiazol-5-thiol in place of 3-t-butyl-1,2,4-thiadiazol-5-thiol, and to the compound thus obtained was added 0.18 g (0.002 mol) of oxalic acid in the presence of ethyl acetate/n-hexane to afford the title compound.
M.p. : 169 to 172 °C
^{1}H-NMR(DMSO-d_6, δ, ppm) 1.29(d, 3H), 4.87(m, 3H), 6.58(s, 1H), 6.67-7.91(m, 7H), 7.67 and 8.30(ss, 2H)

Example 55 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(pyrimidin-5-yl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 1 above were repeated using 0.589 g (0.003 mol) of 3-(pyrimidin-5-yl)-1,2,4-thiadiazol-5-thiol in place of 3-t-butyl-1,2,4-thiadiazol-5-thiol to afford the title compound.
M.p. : 140 to 143 °C
^{1}H-NMR(DMSO-d_6, δ, ppm) 1.30(d, 3H), 4.90(m, 3H), 6.61(s, 1H), 7.00-7.30(m, 3H), 7.88 and 8.28(ss, 2H), 9.35 and 9.41(d, 3H)

Example 56 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(4-biphenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 1 above were repeated using 0.811 g (0.003 mol) of 3-(4-biphenyl)-1,2,4-thiadiazol-5-thiol in place of 3-t-butyl-1,2,4-thiadiazol-5-thiol to afford the title compound.
M.p. : 127 to 129 °C
^{1}H-NMR($CDCl_3$, δ, ppm) 1.40(d, 3H), 4.84(q, 1H), 5.01(dd, 2H), 5.82(s, 1H), 6.70-7.85(m, 12H), 8.38 and 8.41(ss, 2H)

Example 57 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(4-(2,2,3,3-tetrafluoropropoxy)phenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 1 above were repeated using 0.973 g (0.003 mol) of 3-(4-(2,2,3,3-tetrafluoropropoxy)phenyl)-1,2,4-thiadiazol-5-thiol in place of 3-t-butyl-1,2,4-thiadiazol-5-thiol to afford the title compound.
M.p. : 140 to 142 °C
^{1}H-NMR($CDCl_3$, δ, ppm) 1.39(d, 3H), 4.48(q, 1H), 5.09(dd, 2H), 5.82(s, 1H), 5.83, 6.15 and 6.40(t, 1H), 6.75-7.83(m, 7H), 8.27 and 8.32(ss, 2H)

Example 58 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(4-(4-pyridon-1-yl)phenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 1 above were repeated using 0.862 g (0.003 mol) of 3-(4-(4-pyridon-1-yl)phenyl)-1,2,4-thiadiazol-5-thiol in place of 3-t-butyl-1,2,4-thiadiazol-5-thiol to afford the title compound.
M.p. : 235 to 238 °C
^{1}H-NMR(DMSO-d_6, δ, ppm) 1.32(d, 3H), 4.90(q, 3H), 6.33 and 8.11(dd, 4H), 6.66(s, 1H), 6.88-8.37(m, 7H), 7.69 and 8.30(ss, 2H)

Example 59 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(4-methylpyrimidin-2-yl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 1 above were repeated using 0.631 g (0.003 mol) of 3-(4-methylpyrimidin-2-yl)-1,2,4-thiadiazol-5-thiol in place of 3-t-butyl-1,2,4-thiadiazol-5-thiol to afford the title compound.
M.p. : 235 to 238 °C
^{1}H-NMR(DMSO-d_6, δ, ppm) 1.38(d, 3H), 2.65(s, 3H), 4.80(m, 1H), 4.93(s, 2H), 6.77(s, 1H), 7.07-7.38(m, 3H), 7.61 and 8.91(dd, 2H), 7.69 and 8.30(ss, 2H)

Example 60 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(pyridin-N-oxo-4-yl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 1 above were repeated using 0.634 g (0.003 mol) of 3-(pyridin-N-oxo-4-yl)-1,2,4-thiadiazol-5-thiol in place of 3-t-butyl-1,2,4-thiadiazol-5-thiol to afford the title compound.
M.p. : 201 to 204 °C
^{1}H-NMR(DMSO-d_6, δ, ppm) 1.33(d, 3H), 4.70-5.00(m, 3H), 6.67(s, 4H), 6.90-7.10(m, 3H), 7.72 and 8.31(ss, 2H), 8.10-8.40(m, 4H)

Example 61 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(4-methylthiophenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 1 above were repeated using 0.721 g (0.003 mol) of 3-(4-methylthiophenyl)-1,2,4-thiadiazol-5-thiol in place of 3-t-butyl-1,2,4-thiadiazol-5-thiol to afford the title compound.
M.p. : 140 to 143 °C
^{1}H-NMR(DMSO-d_6, δ, ppm) 1.30(d, 3H), 2.67(s, 3H), 4.80(m, 3H), 6.61(s, 1H), 7.00-8.15(m, 7H), 7.00 and 8.30(ss, 2H)

Example 62 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(4-methanesulfonylphenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 1 above were repeated using 0.817 g (0.003 mol) of 3-(4-methanesulfonylphenyl)-1,2,4-thiadiazol-5-thiol in place of 3-t-butyl-1,2,4-thiadiazol-5-thiol to afford the title compound.
M.p. : 172 to 174 °C
^{1}H-NMR(DMSO-d_6, δ, ppm) 1.33(d, 3H), 3.31(s, 3H), 4.90(m, 3H), 6.64(s, 1H), 7.00-8.45(m, 7H), 7.70 and 8.29(ss, 2H)

Example 63 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(3-nitrophenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 1 above were repeated using 0.718 g (0.003 mol) of 3-(3-nitrophenyl)-1,2,4-thiadiazol-5-thiol in place of 3-t-butyl-1,2,4-thiadiazol-5-thiol to afford the title compound.
M.p. : 115 to 118 °C
^{1}H-NMR(DMSO-d_6, δ, ppm) 1.32(d, 3H), 4.88(m, 3H), 6.66(s, 1H), 7.05(m, 1H), 7.32(m, 2H), 7.69(s, 1H), 7.90(t, 1H), 8.29(s, 1H), 8.40 and 8.55(d, 2H)

Example 64 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-

3-[3-(2,5-difluorophenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 1 above were repeated using 0.691 g (0.003 mol) of 3-(2,5-difluorophenyl)-1,2,4-thiadiazol-5-thiol in place of 3-t-butyl-1,2,4-thiadiazol-5-thiol to afford the title compound.

M.p. : 151 to 153 °C

^{1}H-NMR(DMSO-d_6, δ, ppm) 1.31(d, 3H), 4.89(m, 3H), 6.64(s, 1H), 7.05-7.90(m, 3H), 7.70 and 8.31(ss, 2H)

Example 65 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(4-dimethylaminophenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 1 above were repeated using 0.712 g (0.003 mol) of 3-(4-dimethylaminophenyl)-1,2,4-thiadiazol-5-thiol in place of 3-t-butyl-1,2,4-thiadiazol-5-thiol to afford the title compound.

M.p. : 160 to 163 °C

^{1}H-NMR(DMSO-d_6, δ, ppm) 1.31(d, 3H), 3.03(s, 6H), 4.89(m, 3H), 6.61(s, 1H), 6.84-8.05(m, 3H), 7.69 and 8.32(ss, 2H)

Example 66 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(1H-1,2,4-triazol-1-yl)methyl-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 3 above were repeated using 0.640 g (0.003 mol) of 5-chloro-3-bromomethyl-1,2,4-thiadiazole in place of 5-chloro-3-cyclopropyl-1,2,4-thiadiazole and adding 0.364 g (0.004 mol) of triazole·Na salt to the stirred reaction mixture to afford the title compound.

M.p. : 136 to 140 °C

^{1}H-NMR(DMSO-d_6, δ, ppm) 1.23(d, 3H), 3.60(q, 1H), 4.16(q, 2H), 4.78 and 5.06(dd, 2H), 5.10(s, 1H), 6.71-7.50(m, 3H), 7.41, 7.78, 8.19 and 9.14(q, 4H)

Example 67 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(4-methoxystyryl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 3 above were repeated using 0.758 g (0.003 mol) of 5-chloro-3-(4-methoxystyryl)-1,2,4-thiadiazole in place of 5-chloro-3-cyclopropyl-1,2,4-thiadiazole to afford the title compound.

M.p. : 129 to 131 °C

^{1}H-NMR(DMSO-d_6, δ, ppm) 1.06(d, 3H), 3.70(q, 1H), 4.63 and 4.83(dd, 2H), 6.03(s, 1H), 6.38-8.37(dd, 2H), 6.90-7.24(m, 3H), 7.62 and 8.23(ss, 2H)

Example 68 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(3-pyrrol-1-yl)phenyl-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 1 above were repeated using 0.778 g (0.003 mol) of 3-(3-pyrrol-1-yl)phenyl-1,2,4-thiadiazol-5-thiol in place of 3-t-butyl-1,2,4-thiadiazol-5-thiol to afford the title compound.

M.p. : 84 to 86 °C

^{1}H-NMR(DMSO-d_6, δ, ppm) 1.38(d, 3H), 5.02(m, 3H), 6.44(s, 2H), 6.71(s, 1H), 7.10-8.41(m, 11H), 7.75 and 8.38(ss, 2H)

Example 69 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(pyridazin-3-yl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 1 above were repeated using 0.589 g (0.003 mol) of 3-(pyridazin-3-yl)-1,2,4-thiadiazol-5-thiol in place of 3-t-butyl-1,2,4-thiadiazol-5-thiol to afford the title compound.

M.p. : 168 to 170 °C

^{1}H-NMR($CDCl_3$, δ, ppm) 1.38(d, 3H), 4.80(q, 1H), 4.90 and 5.12(dd, 2H), 5.80(s, 1H), 6.75-7.55(m, 3H), 7.65-9.35(m, 3H), 7.78 and 7.90(ss, 2H)

Example 70 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(1-chloro-2-methoxyethyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol·HCl

A mixture of 0.571 g (0.002 mol) of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-mercapto-1-(1H-1,2,4-triazol-1-yl)-2-butanol, 0.636 g (0.003 mol) of 5-chloro-3-(1-chloro-2-methoxyethyl)-1,2,4-thiadiazole and 0.108 g (0.002 mol) of sodium methoxide in 5 ml of methanol was stirred at 0 °C for about 15 minutes. The reaction mixture was processed as in Example 3 above and recystallized from ethyl ether by the addition of HCl-saturated ethyl ether to afford the title compound.

M.p. : 178 to 180 °C

^{1}H-NMR(DMSO-d_6, δ, ppm) 1.27(d, 3H), 3.31(s, 3H), 4.00(m, 2H), 4.74(q, 1H), 4.89(s, 2H), 5.44(m, 1H), 6.90-7.40(m, 3H), 8.00 and 8.82(ss, 2H)

Example 71 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-(3-methoxymethyl-1,2,4-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

A mixture of 0.571 g (0.002 mol) of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-mercapto-1-(1H-1,2,4-triazol-1-yl)-2-butanol, 0.640 g (0.003 mol) of 5-chloro-3-bromomethyl-1,2,4-thiadiazole and 0.324 g (0.006 mol) of sodium methoxide in 5 ml of methanol was stirred at 0 °C for about 15 minutes. The reaction mixture was processed as in Example 3 above to afford the title compound.

M.p. : 73 to 76 °C

^{1}H-NMR($CDCl_3$, δ, ppm) 1.20(d, 3H), 3.55(q, 1H), 3.93(q, 2H), 4.22(s, 3H), 4.72 and 5.03(dd, 2H), 5.15(s, 1H), 6.69-7.45(m, 3H), 7.75 and 7.82(ss, 2H)

Example 72 : Synthesis of (2R, 3R)-2-(2,4-difluorophenyl)-3-(3-styryl-1,2,4-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 3 above were repeated using 0.571 g (0.002 mol) of (2R, 3R)-2-(2,4-difluorophenyl)-3-mercapto-1-(1H-1,2,4-triazol-1-yl)-2-butanol and 0.668 g (0.003 mol) of 5-chloro-3-styryl-1,2,4-thiadiazole in place of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-mercapto-1-(1H-1,2,4-triazol-1-yl)-2-butanol and 5-chloro-3-cyclopropyl-1,2,4-thiadiazole, respectively, to afford the title compound. Thereto was added 0.18 g (0.002 mol) of oxalic acid in the presence of ethyl acetate/n-hexane to afford an oxalate of the title compound. To the title compound was added 0.192 g (0.002 mol) of methanesulfonic acid in the presence of ethylether to afford a methanesulfonate of the title compound.

M.p. : 125 °C (oxalate)

M.p. : 88 to 91 °C (methanesulfonate)

1H-NMR($CDCl_3$, δ, ppm) 1.35(d, 3H), 4.77(q, 1H), 5.05(dd, 2H), 6.73-7.68(dd, 3H), 7.20 and 7.85(dd, 2H), 7.85 and 8.21(ss, 2H)

Example 73 : Synthesis of (2R, 3R)-2-(2,4-difluorophenyl)-3-(3-methoxy-1,2,4-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 5 above were repeated using 0.571 g (0.002 mol) of (2R, 3R)-2-(2,4-difluorophenyl)-3-mercapto-1-(1H-1,2,4-triazol-1-yl)-2-butanol in place of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-mercapto-2-(1H-1,2,4-triazol-1-yl)-2-butanol to afford the title compound. Thereto was added 0.18 g (0.002 mol) of oxalic acid in the presence of ethyl acetate/n-hexane to afford an oxalate of the title compound.

M.p. : 77 to 79 °C

M.p. : 107 to 110 °C (oxalate)

1H-NMR(DMSO-d_6, δ, ppm) 1.21(d, 3H), 4.78(s, 3H), 4.62(q, 1H), 4.78(s, 2H), 6.66(s, 1H), 6.82-7.38(m, 3H), 7.66 and 8.26(ss, 2H)

Example 74 : Synthesis of (2R*, 3R*)-2-(4-chlorophenyl)-3-(3-

methoxy-1,2,4-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 5 above were repeated using 0.568 g (0.002 mol) of (2R*, 3R*)-2-(4-chlorophenyl)-3-mercapto-1-(1H-1,2,4-triazol-1-yl)-2-butanol in place of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-mercapto-2-(1H-1,2,4-triazol-1-yl)-2-butanol to afford the title compound.
M.p. : 93 to 95 °C
1H-NMR(DMSO-d_6, δ, ppm) 1.25(d, 3H), 3.98(s, 3H), 4.30(q, 1H), 4.82(d, 2H), 6.35(s, 1H), 7.33(s, 4H), 7.82 and 8.17(ss, 2H)

Example 75 : Synthesis of (2R*, 3R*)-2-(4-fluorophenyl)-3-(3-methoxy-1,2,4-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 5 above were repeated using 0.535 g (0.002 mol) of (2R*, 3R*)-2-(4-fluorophenyl)-3-mercapto-1-(1H-1,2,4-triazol-1-yl)-2-butanol in place of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-mercapto-2-(1H-1,2,4-triazol-1-yl)-2-butanol to afford the title compound.
M.p. : 111 to 113 °C
1H-NMR(DMSO-d_6, δ, ppm) 1.29(d, 3H), 4.00(s, 3H), 4.43(q, 1H), 4.83(d, 2H), 6.36(s, 1H), 7.17-7.43(m, 4H), 7.86 and 8.19(ss, 2H)

Example 76 : Synthesis of (2R*, 3R*)-2-(4-fluorophenyl)-3-(3-styryl-1,2,4-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 3 above were repeated using 0.535 g (0.002 mol) of (2R*, 3R*)-2-(4-fluorophenyl)-3-mercapto-1-(1H-1,2,4-triazol-1-yl)-2-butanol and 0.668 g (0.003 mol) of 5-chloro-3-styryl-1,2,4-thiadiazole in place of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-mercapto-2-(1H-1,2,4-triazol-1-yl)-2-butanol and 5-chloro-3-cyclopropyl-1,2,4-thiadiazole, respectively, to afford the title compound.

M.p. : 126 to 129 °C
1H-NMR(DMSO-d_6, δ, ppm) 1.35(d, 3H), 4.40(m, 1H), 4.90(dd, 2H), 6.30(s, 1H), 7.20-7.80(m, 11H), 7.89 and 8.24(ss, 2H)

Example 77 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[4-(2,6-difluorophenyl)-thiazol-2-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 1 above were repeated using 0.688 g (0.003 mol) of 4-(2,6-difluorophenyl)-thiazol-2-thiol in place of 3-t-butyl-1,2,4-thiadiazol-5-thiol to afford the title compound.
M.p. : 131 to 133 °C
^{1}H-NMR($CDCl_3$, δ, ppm) 1.30(d, 3H), 4.25(q, 1H), 5.02(dd, 2H), 6.62-7.56(m, 7H), 7.66 and 8.12(ss, 2H)

Example 78 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[4-(2,4-dichlorophenyl)-thiazol-2-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 1 above were repeated using 0.787 g (0.003 mol) of 4-(2,4-dichlorophenyl)-thiazol-2-thiol in place of 3-t-butyl-1,2,4-thiadiazol-5-thiol to afford the title compound.
M.p. : 138 to 140 °C
^{1}H-NMR(DMSO-d_6, δ, ppm) 1.24(d, 3H), 4.78(q, 1H), 4.89(s, 2H), 6.49(s, 1H), 6.80-7.92(m, 6H), 8.10 and 8.30(ss, 2H)

Example 79 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[4-(4-chlorophenyl)-thiazol-2-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 1 above were repeated using 0.683 g (0.003 mol) of 4-(4-chlorophenyl)-thiazol-2-thiol in place of 3-t-butyl-1,2,4-thiadiazol-5-thiol to afford the title compound.
M.p. : 115 to 117 °C
^{1}H-NMR($CDCl_3$, δ, ppm) 1.30(d, 3H), 4.44(q, 1H), 5.01(dd, 2H),

6.59(s, 1H), 6.65-7.85(m, 8H), 7.95(s, 1H)

Example 80 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-(4-ethylthiazol-2-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol·oxalate

The same procedures as in Example 1 above were repeated using 0.436 g (0.003 mol) of 4-ethylthiazol-2-thiol in place of 3-t-butyl-1,2,4-thiadiazol-5-thiol and to the compound thus obtained was added 0.18 g (0.002 mol) of oxalic acid in the presence of ethyl acetate/n-hexane to afford the title compound.

M.p. : 108 to 110 °C

^{1}H-NMR($CDCl_3$, δ, ppm) 1.24(d, 3H), 1.34(t, 3H), 2.85(q, 2H), 4.03(q, 1H), 5.03(dd, 2H), 6.70-7.60(m, 3H), 7.88 and 8.63(ss, 2H)

Example 81 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[4-(1-hydroxy-1-methylethyl)-thiazol-2-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol·oxalate

The same procedures as in Example 1 above were repeated using 0.526 g (0.003 mol) of 4-(1-hydroxy-1-methylethyl)-thiazol-2-thiol in place of 3-t-butyl-1,2,4-thiadiazol-5-thiol and to the compound thus obtained was added 0.18 g (0.002 mol) of oxalic acid in the presence of ethyl acetate/n-hexane to afford the title compound.

M.p. : 106 to 108 °C

^{1}H-NMR(DMSO-d_6, δ, ppm) 1.17(d, 3H), 1.47(t, 3H), 4.67(q, 1H), 4.83(dd, 2H), 6.50(s, 1H), 6.87-7.31(m, 3H), 7.32(s, 1H), 7.63 and 8.31(ss, 2H)

Example 82 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-(4-styrylthiazol-2-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 1 above were repeated using 0.658 g (0.003 mol) of 4-styrylthiazol-2-thiol in

place of 3-t-butyl-1,2,4-thiadiazol-5-thiol to afford the title compound.

M.p. : 98 to 100 °C

^{1}H-NMR($CDCl_3$, δ, ppm) 1.31(d, 3H), 4.40(q, 1H), 5.07(dd, 2H), 6.70-7.60(m, 11H), 7.72 and 8.05(ss, 2H)

Example 83 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[4-(4-methoxystyryl)-thiazol-2-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 1 above were repeated using 0.748 g (0.003 mol) of 4-(4-methoxystyryl)-thiazol-2-thiol in place of 3-t-butyl-1,2,4-thiadiazol-5-thiol to afford the title compound.

M.p. : 138 to 140 °C

^{1}H-NMR($CDCl_3$, δ, ppm) 1.31(d, 3H), 3.85(s, 3H), 4.38(q, 1H), 5.02(dd, 2H), 6.70-7.60(m, 10H), 7.71 and 8.05(ss, 2H)

Example 84 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[4-(2,3-dichlorostyryl)-thiazol-2-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 1 above were repeated using 0.865 g (0.003 mol) of 4-(2,3-dichlorostyryl)-thiazol-2-thiol in place of 3-t-butyl-1,2,4-thiadiazol-5-thiol to afford the title compound.

M.p. : 135 to 137 °C

^{1}H-NMR($CDCl_3$, δ, ppm) 1.33(d, 3H), 4.05(q, 1H), 5.07(dd, 2H), 6.60(s, 1H), 6.65-7.70(m, 7H), 7.91 and 8.01(ss, 2H)

Example 85 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-(1,2,3-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

A mixture of 0.502 g (0.002 mol) of (2R*, 3S*)-2-(2,4-difluorophenyl)-3-methyl-2-[(1H-1,2,4-triazol-1-yl)methyl]oxirane, 0.420 g (0.003 mol) of 1,2,3-thiadiazol-5-thiol·Na salt and 0.319 g (0.003 mol) of lithium

perchlorate in 6 ml of acetonitrile was stirred at 100 °C for 12 hours. The reaction mixture was diluted with 100 ml of ethyl acetate, and washed with 5% sodium hydroxide aqueous solution (30 ml x 2) and then saline (30 ml x 1). The organic layer was dried over anhydrous magnesium sulfate and evaporated under reduced pressure to give a residue, which was purified by silica gel column chromatography to afford the title compound.

M.p. : 129 to 131.5 °C

^{1}H-NMR(DMSO-d_6, δ, ppm) 1.26(d, 3H), 4.20(q, 1H), 4.94(s, 2H), 6.73(s, 1H), 7.08-7.44(m, 3H), 7.82 and 8.35(ss, 2H), 9.05(s, 1H)

Example 86 : Synthesis of (2R*, 3R*)-2-(4-chlorophenyl)-3-(1,2,3-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 85 above were repeated using 0.499 g (0.002 mol) of (2R*, 3S*)-2-(4-chlorophenyl)-3-methyl-2-[(1H-1,2,4-triazol-1-yl)methyl]oxirane and 0.420 g (0.003 mol) of 1,2,3-thiadiazol-5-thiol·Na salt to afford the title compound.

M.p. : 151 to 153 °C

^{1}H-NMR(DMSO-d_6, δ, ppm) 1.27(d, 3H), 4.20(q, 1H), 4.96(s, 2H), 6.46(s, 1H), 7.48(m, 4H), 7.96 and 8.28(ss, 2H), 9.04(s, 1H)

Example 87 : Synthesis of (2R*, 3R*)-2-(2,4-dichlorophenyl)-3-(1,2,3-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 85 above were repeated using 0.568 g (0.002 mol) of (2R*, 3S*)-2-(2,4-dichlorophenyl)-3-methyl-2-[(1H-1,2,4-triazol-1-yl)methyl]oxirane and 0.420 g (0.003 mol) of 1,2,3-thiadiazol-5-thiol·Na salt to afford the title compound.

M.p. : 158 to 160 °C

^{1}H-NMR(DMSO-d_6, δ, ppm) 1.18(d, 3H), 4.65(q, 1H), 5.10(dd,

2H), 6.78(s, 1H), 7.36-7.60(m, 3H), 7.67 and 8.34(ss, 2H), 9.01(s, 1H)

Example 88 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-(4-methyl-1,2,3-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 85 above were repeated using 0.502 g (0.002 mol) of (2R*, 3S*)-2-(2,4-difluorophenyl)-3-methyl-2-[(1H-1,2,4-triazol-1-yl)methyl]oxirane and 0.463 g (0.003 mol) of 4-methyl-1,2,3-thiadiazol-5-thiol·Na salt to afford the title compound.
M.p. : 135 to 137 °C
^{1}H-NMR(DMSO-d_6, δ, ppm) 1.14(d, 3H), 2.61(s, 3H), 4.00(q, 1H), 4.95(m, 2H), 6.63(s, 1H), 7.00-7.30(m, 3H), 7.72 and 8.26(ss, 2H)

Example 89 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-(4-phenyl-1,2,3-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 85 above were repeated using 0.502 g (0.002 mol) of (2R*, 3S*)-2-(2,4-difluorophenyl)-3-methyl-2-[(1H-1,2,4-triazol-1-yl)methyl]oxirane and 0.649 g (0.003 mol) of 4-phenyl-1,2,3-thiadiazol-5-thiol·Na salt to afford the title compound.
M.p. : 96 to 98 °C
^{1}H-NMR(DMSO-d_6, δ, ppm) 1.19(d, 3H), 4.10(m, 1H), 4.82(m, 2H), 6.73(s, 1H), 7.05-7.50(m, 6H), 7.74 and 8.27(ss, 2H), 7.90(s, 2H)

Example 90 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[4-(2,4-difluorophenyl)-1,2,3-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol oxalate

The same procedures as in Example 85 above were repeated using 0.502 g (0.002 mol) of (2R*, 3S*)-2-(2,4-difluoroph nyl)-3-methyl-2-[(1H-1,2,4-triazol-1-

yl)methyl]oxirane and 0.753 g (0.003 mol) of 4-(2,4-difluorophenyl)-1,2,3-thiadiazol-5-thiol·Na salt, and thereto was added 0.19 g (0.002 mol) of oxalic acid in the presence of ethyl acetate/n-hexane to afford the title compound.

M.p. : 111 to 113 °C

^{1}H-NMR(DMSO-d_6, δ, ppm) 1.34(d, 3H), 4.05(q, 1H), 4.76(s, 2H), 6.65(s, 1H), 7.00-7.80(m, 6H), 7.73 and 8.25(ss, 2H)

Example 91 : Synthesis of (2R*, 3R*)-2-(4-fluorophenyl)-3-(1,2,3-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol oxalate

The same procedures as in Example 90 above were repeated using 0.467 g (0.002 mol) of (2R*, 3S*)-2-(4-fluorophenyl)-3-methyl-2-[(1H-1,2,4-triazol-1-yl)methyl]oxirane and 0.463 g (0.003 mol) of 1,2,3-thiadiazol-5-thiol·Na salt to afford the title compound.

M.p. : 138 to 140 °C

^{1}H-NMR(DMSO-d_6, δ, ppm) 1.80(d, 3H), 4.00(q, 1H), 4.83(dd, 2H), 6.30(s, 1H), 7.10-7.30(m, 4H), 7.85 and 8.16(ss, 2H), 8.89(s, 1H)

Example 92 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(N-morpholinyl)-1,2,5-thiadiazol-4-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

A mixture of 0.571 g (0.002 mol) of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-mercapto-1-(1H-1,2,4-triazol-1-yl)-2-butanol, 0.617 g (0.003 mol) of 4-chloro-3-(N-morpholinyl)-1,2,5-thiadiazole and 0.072 g (0.003 mol) of NaH in 6 ml of dimethoxyethane was stirred at 25 °C for 1 hour. The reaction mixture was diluted with 100 ml of ethyl acetate, and washed with 5% sodium hydroxide aqueous solution (30 ml x 2) and saline (30 ml x 1). The organic layer was dried over anhydrous magnesium sulfate and evaporated under reduced pressure to give a residue, which was purified by silica gel column chromatography and recrystallized from

isopropyl ether to afford the title compound.
M.p. : 155 to 158 °C
^{1}H-NMR($CDCl_3$, δ, ppm) 1.25(d, 3H), 3.45(m, 4H), 3.87(m, 4H), 4.75(q, 1H), 5.00(dd, 2H), 5.40(s, 1H), 6.80-7.40(m, 3H), 7.80(s, 2H)

Example 93 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(N-thiomorpholinyl)-1,2,5-thiadiazol-4-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 92 above were repeated using a mixture of 0.571 g (0.002 mol) of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-mercapto-1-(1H-1,2,4-triazol-1-yl)-2-butanol, 0.665 g (0.003 mol) of 4-chloro-3-(N-thiomorpho-linyl)-1,2,5-thiadiazole and 0.072 g (0.003 mol) of NaH in 6 ml of dimethoxyethane to afford the title compound.
M.p. : 133 to 135 °C
^{1}H-NMR($CDCl_3$, δ, ppm) 1.25(d, 3H), 3.81(m, 4H), 3.71(m, 4H), 4.70(m, 1H), 4.95(dd, 2H), 5.39(s, 1H), 6.75-7.35(m, 3H), 7.77(s, 2H)

Example 94 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(piperidin-1-yl)-1,2,5-thiadiazol-4-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol·HCl

The same procedures as in Example 92 above were repeated using a mixture of 0.571 g (0.002 mol) of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-mercapto-1-(1H-1,2,4-triazol-1-yl)-2-butanol, 0.611 g (0.003 mol) of 4-chloro-3-(piperidin-1-yl)-1,2,5-thiadiazole and 0.162 g (0.003 mol) of MeONa in 6 ml of methanol, and, thereafter, the compound thus obtained was recrystallized from ethyl ether by the addition of 5 ml of HCl-saturated ethyl ether to afford the title compound.
M.p. : 70 to 73 °C
^{1}H-NMR($CDCl_3$, δ, ppm) 1.25(d, 3H), 1.65(m, 6H), 3.40(m, 2H), 3.50(dd, 2H), 4.70(dd, 1H), 5.00(dd, 2H), 5.50(s, 1H), 6.80-

7.40(m, 3H), 7.77 and 7.82(ss, 2H)

Example 95 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(pyrrolidin-1-yl)-1,2,5-thiadiazol-4-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 92 above were repeated using a mixture of 0.571 g (0.002 mol) of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-mercapto-1-(1H-1,2,4-triazol-1-yl)-2-butanol, 0.569 g (0.003 mol) of 4-chloro-3-(pyrrolidin-1-yl)-1,2,5-thiadiazole and 0.072 g (0.003 mol) of NaH in 6 ml of acetonitrile to afford the title compound.
M.p. : 139 to 141 °C
^{1}H-NMR($CDCl_3$, δ, ppm) 1.25(d, 3H), 1.99(m, 4H), 3.75(m, 4H), 4.65(dd, 1H), 5.00(dd, 2H), 5.30(s, 1H), 6.75-7.40(m, 3H), 7.77 and 7.82(ss, 2H)

Example 96 : Synthesis of (2R, 3R)-2-(2,4-difluorophenyl)-3-[3-(N-thiomorpholinyl)-1,2,5-thiadiazol-4-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

The same procedures as in Example 92 above were repeated using a mixture of 0.571 g (0.002 mol) of (2R, 3R)-2-(2,4-difluorophenyl)-3-mercapto-1-(1H-1,2,4-triazol-1-yl)-2-butanol, 0.665 g (0.003 mol) of 4-chloro-3-(N-thiomorpholinyl)-1,2,5-thiadiazole and 0.162 g (0.003 mol) of MeONa in 6 ml of methanol to afford the title compound.
M.p. : 83 to 86 °C
^{1}H-NMR($CDCl_3$, δ, ppm) 1.27(d, 3H), 2.83(m, 4H), 3.73(m, 4H), 4.73(q, 1H), 5.00(dd, 2H), 5.41(s, 1H), 6.70-7.50(m, 3H), 7.81 and 7.84(ss, 2H)

Example 97 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-(1,2-benzoisothiazol-3-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

To a suspension of 0.50 g (0.00175 mol) of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-mercapto-1-(1H-1,2,4-triazol-1-yl)-2-

butanol and 0.59 g (0.0035 mol) of 3-chloro-1,2-benzoisothiazole in 4 ml of acetonitrile was added dropwise 1 ml of triethylamine at room temperature. The resulting mixture was stirred for 1 hour and evaporated to obtain a concentrate, which was diluted with 100 ml of ethyl acetate, and washed with 5% sodium hydroxide aqueous solution (30 ml x 2) and then saline (30 ml x 1). The organic layer was dried over anhydrous magnesium sulfate and evaporated under reduced pressure to give a residue, which was purified by silica gel column chromatography to afford the title compound.

M.p. : 133 to 135 °C

^{1}H-NMR(DMSO-d_6, δ, ppm) 1.13(d, 3H), 3.71(q, 1H), 4.81(dd, 2H), 6.40(s, 1H), 6.85-8.05(m, 7H), 7.65 and 8.25(ss, 2H)

Example 98 : Synthesis of (2R, 3R)-2-(2,4-difluorophenyl)-3-(1,2-benzoisothiazol-3-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

To a suspension of 0.50 g (0.00175 mol) of (2R, 3R)-2-(2,4-difluorophenyl)-3-mercapto-1-(1H-1,2,4-triazol-1-yl)-2-butanol and 0.36 g (0.0021 mol) of 3-chloro-1,2-benzoisothiazole in 6 ml of acetonitrile was added dropwise 1 ml of triethylamine at 3 ± 2 °C. The resultant was processed as in Example 97 above to afford the title compound.

M.p. : 128 to 130 °C

^{1}H-NMR($CDCl_3$, δ, ppm) 1.18(d, 3H), 3.58(q, 1H), 4.90-5.10(m, 3H), 6.66-7.95(m, 7H), 7.84 and 8.50(ss, 2H)

To a solution of 0.42 g (0.001 mol) of the title compound in 10 ml of ethyl acetate was added 0.11 g (0.0012 mol) of oxalic acid, and the resulting mixture was heated to dissolve completely. To the resulting solution was added dropwise n-hexane to afford an oxalate of the title compound.

M.p. : 82 to 85 °C (oxalate)

To a solution of 0.42 g (0.001 mol) of the title compound in 10 ml of ethyl ether was added 10 ml of HCl-

saturated ethyl ether to afford a hydrochloride of the title compound.
M.p. : 87 to 90 °C (HCl)

Example 99 : Synthesis of (2R*, 3R*)-2-(4-chlorophenyl)-3-(1,2-benzoisothiazol-3-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol oxalate

To a suspension of 0.60 g (0.0021 mol) of (2R*, 3R*)-2-(4-chlorophenyl)-3-mercapto-1-(1H-1,2,4-triazol-1-yl)-2-butanol and 0.36 g (0.0021 mol) of 3-chloro-1,2-benzoisothiazole in 6 ml of acetonitrile was added slowly dropwise 1 ml of triethylamine at 3 ± 2 °C. The resultant was stirred for 20 minutes, and processed as in Example 97 above. The compound thus obtained was dissolved in ethyl acetate, and to the resulting solution was added 0.22 g (0.0024 mol) of oxalic acid and the resultant was heated to dissolve completely. To the resulting solution was added dropwise n-hexane to afford the title compound.
M.p. : 80 to 83 °C
^{1}H-NMR(DMSO-d_6, δ, ppm) 1.10(d, 3H), 3.70(q, 1H), 4.80(dd, 2H), 6.10(s, 1H), 7.32-7.90(m, 8H), 7.76 and 8.17(ss, 2H)

Example 100 : Synthesis of (2R*, 3R*)-2-(4-fluorophenyl)-3-(1,2-benzoisothiazol-3-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol oxalate

To a suspension of 0.50 g (0.00187 mol) of (2R*, 3R*)-2-(4-fluorophenyl)-3-mercapto-1-(1H-1,2,4-triazol-1-yl)-2-butanol and 0.32 g (0.00187 mol) of 3-chloro-1,2-benzoisothiazole in 6 ml of acetonitrile was added slowly dropwise 0.5 ml of triethylamine with cooling at an ice bath. The resultant was stirred at room temperature for 20 minutes, and processed as in Example 97 above. The obtained compound was dissolved in ethyl acetate, and to the resulting solution was added 0.22 g (0.0024 mol) of oxalic acid and heated to dissolve completely. To the resulting solution was added ethyl ether to afford the title compound.

M.p. : 138 to 140 °C
^{1}H-NMR(DMSO-d_6, δ, ppm) 1.14(d, 3H), 3.65(m, 1H), 4.85(dd, 2H), 6.10(s, 1H), 7.10-7.91(m, 8H), 7.80 and 8.19(ss, 2H)

Example 101 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-(5-chloro-1,2-benzoisothiazol-3-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

To a suspension of 0.70 g (0.00245 mol) of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-mercapto-1-(1H-1,2,4-triazol-1-yl)-2-butanol and 0.82 g (0.0040 mol) of 3,5-dichloro-1,2-benzoisothiazole in 10 ml of acetonitrile was added slowly dropwise 1.5 ml of triethylamine with cooling at an ice bath. The resultant was stirred for 1 hour and processed as in Example 97 above to afford the title compound.
M.p. : 154 to 156 °C
^{1}H-NMR($CDCl_3$, δ, ppm) 1.15(d, 3H), 3.56(q, 1H), 4.97(dd, 2H), 5.21(s, 1H), 6.65-7.78(m, 6H), 7.79 and 7.81(ss, 2H)

Example 102 : Synthesis of (2R*, 3R*)-2-(4-chlorophenyl)-3-(5-chloro-1,2-benzoisothiazol-3-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

To a suspension of 0.50 g (0.00176 mol) of (2R*, 3R*)-2-(4-chlorophenyl)-3-mercapto-1-(1H-1,2,4-triazol-1-yl)-2-butanol and 0.51 g (0.0025 mol) of 3,5-dichloro-1,2-benzoisothiazole in 6 ml of acetonitrile was added slowly dropwise 1 ml of triethylamine with cooling at an ice bath. The resultant was stirred at room temperature for 30 minutes and processed as in Example 97 above to afford the title compound.
M.p. : 105 to 107 °C
^{1}H-NMR(DMSO-d_6, δ, ppm) 1.15(d, 3H), 3.68(q, 1H), 4.83(dd, 2H), 6.13(s, 1H), 7.33-8.10(m, 7H), 7.80 and 8.19(ss, 2H)

Example 103 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-(5,6-dimethoxy-1,2-benzoisothiazol-3-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

To a suspension of 0.60 g (0.00210 mol) of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-mercapto-1-(1H-1,2,4-triazol-1-yl)-2-butanol and 0.69 g (0.003 mol) of 3-chloro-5,6-dimethoxy-1,2-benzoisothiazole in 10 ml of acetonitrile was added slowly dropwise 1.5 ml of triethylamine with cooling at an ice bath. The resultant was stirred at room temperature for 30 minutes and processed as in Example 97 above to afford the title compound.

M.p. : 157 to 160 °C

^{1}H-NMR($CDCl_3$, δ, ppm) 1.15(d, 3H), 3.62(q, 1H), 3.92 and 3.99(ss, 6H), 4.95(s, 2H), 6.65-7.36(m, 5H), 7.78(ss, 2H)

Example 104 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-(5-methyl-1,2-benzoisothiazol-3-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

To a suspension of 0.80 g (0.0028 mol) of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-mercapto-1-(1H-1,2,4-triazol-1-yl)-2-butanol and 0.64 g (0.0035 mol) of 3-chloro-5-methyl-1,2-benzoisothiazole in 10 ml of acetonitrile was added slowly dropwise 1.5 ml of triethylamine with cooling at an ice bath. The resultant was stirred at room temperature for 30 minutes and processed as in Example 97 above to afford the title compound.

M.p. : 150 to 153 °C

^{1}H-NMR($CDCl_3$, δ, ppm) 1.19(d, 3H), 2.44(s, 3H), 3.62(q, 1H), 5.00(s, 2H), 5.10(s, 1H), 6.65-7.90(m+s, 8H)

Example 105 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-(7-chloro-1,2-benzoisothiazol-3-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

To a suspension of 0.70 g (0.00245 mol) of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-mercapto-1-(1H-1,2,4-triazol-1-yl)-2-butanol and 0.82 g (0.004 mol) of 3,7-dichloro-1,2-benzoisothiazole in 10 ml of acetonitrile was added slowly dropwise 1.5 ml of triethylamine with cooling at an ice bath. The resultant was stirred at room temperature for 18

hours and processed as in Example 97 above to afford the title compound.

M.p. : 126 to 128 °C

^{1}H-NMR($CDCl_3$, δ, ppm) 1.04(d, 3H), 3.48(q, 1H), 4.75-5.10(m, 3H), 6.55-7.85(m, 6H), 7.67(s, 2H)

Example 106 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-(thieno[3,4-d]isothiazol-3-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

To a solution of 1.0 g (0.0035 mol) of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-mercapto-1-(1H-1,2,4-triazol-1-yl)-2-butanol and 1.23 g (0.007 mol) of 3-chlorothieno[3,4-d]isothiazole in 15 ml of acetonitrile was added slowly dropwise 1.5 ml of triethylamine with cooling at an ice bath. The resultant was stirred at room temperature for 1 hour and processed as in Example 97 above to afford the title compound.

M.p. : 82 to 84 °C

^{1}H-NMR($CDCl_3$, δ, ppm) 1.13(d, 3H), 3.64(q, 1H), 4.88(s, 2H), 5.05(s, 1H), 6.60-7.40(m, 3H), 7.64 and 8.04(ss, 2H), 7.77(s, 2H)

Example 107 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-(1,2-benzoisothiazol-1,1-dioxo-3-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

To a solution of 0.70 g (0.00245 mol) of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-mercapto-1-(1H-1,2,4-triazol-1-yl)-2-butanol and 0.99 g (0.0049 mol) of 3-chloro-1,2-benzoisothiazol-1,1-dioxide in 10 ml of acetonitrile was added slowly dropwise 1.5 ml of triethylamine with cooling at an ice bath. The resultant was stirred at room temperature for 3 hours and processed as in Example 97 above to afford the title compound.

M.p. : 213 to 217 °C

^{1}H-NMR(DMSO-d_6, δ, ppm) 1.27(d, 3H), 4.81(s, 2H), 4.91(s, 1H), 6.80(s, 1H), 6.90-8.21(m, 7H), 7.67 and 8.28(ss, 2H)

Example 108 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-(thieno[3,4-d]isothiazol-1,1-dioxo-3-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

A solution of 0.50 g (0.002 mol) of (2R*, 3S*)-2-(2,4-difluorophenyl)-3-methyl-2-[(1H-1,2,4-triazol-1-yl)methyl]oxirane, 0.57 g (0.003 mol) of 3-mercapto-thieno[3,4-d]isothiazol-1,1-dioxide and 0.42 g (0.004 mol) of lithium perchlorate in 6 ml of acetonitrile was heated to reflux at 120 °C for 16 hours with stirring, and processed as in Example 97 above to afford the title compound.

M.p. : 149 to 151 °C

^{1}H-NMR($CDCl_3$, δ, ppm) 1.27(d, 3H), 4.94(dd+q, 3H), 5.54(s, 1H), 6.67-7.40(m, 3H), 7.62-7.88(m, 4H)

Example 109 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-(2,1-benzoisothiazol-3-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

<method 1>

To a solution of 0.57 g (0.002 mol) of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-mercapto-1-(1H-1,2,4-triazol-1-yl)-2-butanol and 0.47 g (0.0022 mol) of 3-bromo-2,1-benzoisothiazole in 6 ml of methanol was added 0.27 g (0.005 mol) of sodium methoxide. The resultant was heated to reflux for 10 minutes with stirring, and processed as in Example 97 above to afford the title compound.

M.p. : 91 to 93 °C

^{1}H-NMR(DMSO-d_6, δ, ppm) 1.19(d, 3H), 4.10(q, 1H), 4.95 and 5.06(dd, 2H), 6.65(s, 1H), 7.00-7.92(m, 7H), 7.74 and 8.34(ss, 2H)

<method 2>

A solution of 0.50 g (0.002 mol) of (2R*, 3S*)-2-(2,4-difluorophenyl)-3-methyl-2-[(1H-1,2,4-triazol-1-yl)methyl]oxiran , 0.50 g (0.003 mol) of 3-mercapto-2,1-

benzoisothiazole and 0.42 g (0.004 mol) of lithium perchlorate in 6 ml of acetonitrile was heated to reflux at 100 °C for 15 hours with stirring, and processed as in Example 97 above to afford the title compound.

Example 110 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-(5-nitro-2,1-benzoisothiazol-3-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

To a solution of 0.57 g (0.002 mol) of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-mercapto-1-(1H-1,2,4-triazol-1-yl)-2-butanol and 0.57 g (0.0022 mol) of 3-bromo-5-nitro-2,1-benzoisothiazole in 6 ml of methanol was added 0.27 g (0.005 mol) of sodium methoxide. The resultant was stirred at room temperature for 30 minutes, and processed as in Example 97 above to afford the title compound.

M.p. : 142 to 144 °C

^{1}H-NMR(DMSO-d_6, δ, ppm) 1.28(d, 3H), 4.40(m, 1H), 4.94(m, 2H), 6.83(s, 1H), 7.00-8.31(m, 6H), 7.77 and 8.74(ss, 2H)

Example 111 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-(isothiazolo[3,4-b]pyridin-3-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

To a solution of 0.57 g (0.002 mol) of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-mercapto-1-(1H-1,2,4-triazol-1-yl)-2-butanol and 0.43 g (0.002 mol) of 3-bromoisothiazolo[3,4-b]pyridine in 10 ml of acetonitrile was added slowly dropwise 1.5 ml of triethylamine with cooling at an ice bath. The resultant was stirred for 15 minutes, and processed as in Example 97 above to afford the title compound.

M.p. : 148 to 150 °C

^{1}H-NMR($CDCl_3$, δ, ppm) 1.26(d, 3H), 3.91(q, 1H), 5.05 and 5.18(dd, 2H), 5.55(s, 1H), 6.73-8.96(m, 7H), 7.85(s, 2H)

Example 112 : Synthesis of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-(1,2-benzoisoxazol-3-yl)thio-1-(1H-1,2,4-

triazol-1-yl)-2-butanol oxalate

To a solution of 0.60 g (0.0023 mol) of (2R*, 3R*)-2-(2,4-difluorophenyl)-3-mercapto-1-(1H-1,2,4-triazol-1-yl)-2-butanol and 0.70 g (0.00464 mol) of 3-chloro-1,2-benzoisoxazole in 10 ml of methanol was added 0.1 g of potassium iodide and 0.27 g (0.005 mol) of sodium methoxide. The resultant was heated to reflux for 15 hours with stirring, and processed as in Example 97 above to afford the title compound.

M.p. : 80 to 82 °C

^{1}H-NMR(DMSO-d_6, δ, ppm) 1.25(d, 3H), 4.86(m, 3H), 6.60(s, 1H), 7.00-7.50(m, 7H), 7.65 and 8.29(ss, 2H)

Example 113 : Synthesis of (2R, 3R)-2-(2,4-difluorophenyl)-3-(thieno[3,4-d]isothiazol-3-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol

To a solution of 0.5 g (0.00175 mol) of (2R, 3R)-2-(2,4-difluorophenyl)-3-mercapto-1-(1H-1,2,4-triazol-1-yl)-2-butanol and 0.6 g (0.0035 mol) of 3-chlorothieno[3,4-d]isothiazole in 15 ml of acetonitrile was added slowly dropwise 1 ml of triethylamine with cooling at an ice bath. The resultant was stirred at room temperature for 1 hour, and processed as in Example 97 above to afford the title compound.

M.p. : 129 to 131 °C

^{1}H-NMR($CDCl_3$, δ, ppm) 1.13(d, 3H), 3.64(q, 1H), 4.88(s, 2H), 5.05(s, 1H), 6.60-7.40(m, 3H), 7.64 and 8.04(dd, 2H), 7.77(s, 2H)

Activity Test

The compounds of formula (I) of the present invention were tested to measure their antifungal activities as follows.

1. syst mic candidosis in mice

Male ICR mice (22 to 25 g) were divided into 48 groups, each consisting of ten mice. The first was a control group employing no test compound, the second was a comparative group employing Fluconazole, a commercially available triazolic antifungal agent, and the 3rd to 48th were employed the compounds of the present invention. Candida albicans B02630 was cultured in SDA medium for 24 hours, and then suspended in a sterilized saline in a concentration of 4.0×10^7 CFU/ml.

All the test animals were infected by injecting 0.2 ml of the fungi suspension into tail vein. Immediately after the injection, Fluconazole and the inventive compounds dissolved in polyethylene glycol 200 were administered orally in an amount of 2 mg/kg into the second group and the 3rd-48th group, respectively. The test compounds were administered three times at an interval of 24 hours. The number of the mice survived was counted at 24 hour interval and the results are shown in Table 5.

Table 5

Group	Compound	Survival Rate (%)		
		1 day	4 days	7 days
1	-	0-100	0-20	0
2	Fluconazole	100	90-100	80-90
3	Ex. 3	100	100	100
4	Ex. 4	100	100	100
5	Ex. 5	100	100	100
6	Ex. 6	100	90	90
7	Ex. 7	100	100	100
8	Ex. 9	100	100	100
9	Ex. 10	100	80	80
10	Ex. 13	100	100	100
11	Ex. 19	100	100	100
12	Ex. 20	100	100	100
13	Ex. 21	100	100	70
14	Ex. 22	100	100	90
15	Ex. 34	100	90	90
16	Ex. 41	100	100	100
17	Ex. 47	100	80	80
18	Ex. 55	100	100	90
19	Ex. 57	100	100	100
20	Ex. 60	100	100	100
21	Ex. 63	100	100	100
22	Ex. 64	100	90	90
23	Ex. 69	100	100	90
24	Ex. 70	100	90	90
25	Ex. 71	100	100	100
26	Ex. 72	100	100	100
27	Ex. 73	100	100	100
28	Ex. 77	100	80	80
29	Ex. 80	100	90	90
30	Ex. 83	100	80	80
31	Ex. 84	100	80	80
32	Ex. 85	100	90	90
33	Ex. 92	100	100	100
34	Ex. 93	100	100	80
35	Ex. 94	100	100	100
36	Ex. 95	100	100	100
37	Ex. 96	100	100	100
38	Ex. 97	100	100	90
39	Ex. 98	100	100	100
40	Ex. 99	100	90	90
41	Ex. 101	100	100	100
42	Ex. 102	100	100	80
43	Ex. 103	100	100	100
44	Ex. 104	100	100	80
45	Ex. 106	100	100	100
46	Ex. 107	100	100	90
47	Ex. 108	100	100	90
48	Ex. 111	100	100	100

2. Effectiveness against fungal infections

A. ED_{50} against candida albicans

Male ICR mice (22 to 25 g) of 36 groups, each group consisting of eight mice, were infected by Candida albicans in accordance with the same procedures as described previously. Immediately after the infection, the inventive compound (prepared in Example 5 of the present invention) dissolved in polyethylene glycol 200 was administered orally in each amount of 20, 10, 5, 2.5 and 1.25 mg/kg into the 2nd-6th group five times at an interval of 24 hours. No compound was administered into the first group. The inventive compounds prepared in Example 47, 72, 73, 93, 97 and 98 were also administered orally into the remaining 7th-36th groups in each amount of 20, 10, 5, 2.5 and 1.25 mg/kg. The number of the mice survived was counted at 24 hour interval.

Separately, the above procedures were repeated using Fluconazole as a comparative compound. After 14 days, the ED_{50} value was calculated from the number of the mice survived in accordance with Litchfield-Wilcoxon method, and the results are shown in Table 6.

B. ED_{50} against by cryptococcus neoformans

Male ICR mice (22 to 25 g) were divided into 36 groups, each group consisting of eight mice. Cryptococcus neoformans IFM 40092 was cultured in SDA medium for 24 hours, and then suspended in a sterilized saline in a concentration of 2.0×10^8 CFU/ml. To each group cyclophosphamide as a immunosuppressive agent was administered intraperitoneally in an amount of 2 mg/mouse. 24 hours after the administration, each group was infected by injecting into tail vein 0.2 ml of the fungi suspension. 2 hours after the infection, the inventive compounds prepared in Example 5, 47, 72, 73, 93, 97 and 98 of the present invention were administered into the the test

animals in each amount of 20, 10, 5, 2.5 and 1.25 mg/kg as described previously. The ED_{50} values measured are shown in Table 6.

C. ED_{50} against Aspergillus fumigatus

Male ICR mice (22 to 25 g) were divided into 36 groups, each group consisting of eight mice. To each group cyclophosphamide (immunosuppressive agent) was administered intraperitoneally in an amount of 2 mg/mouse. 24 hours after the administration, each group was infected by injecting into tail vein 0.2 ml of a suspension of Aspergillus fumigatus B19119 spore (2.0×10^6 CFU/ml in a sterilized saline). 48 hours after the infection, the inventive compounds prepared in Example 5, 47, 72, 73, 93, 97 and 98 of the present invention were administered into the the test animals in each amount of 100, 50, 25, 12.5 and 6.25 mg/kg as described previously. The ED_{50} values measured are shown in Table 6.

Table 6

Compound	ED_{50} (mg/kg)		
	Run A	Run B	Run C
Fluconazole	13.15	> 50.00	> 100.00
Ex. 5	5.83	8.64	20.32
Ex. 47	4.95	9.10	> 80
Ex. 72	4.65	5.06	22.10
Ex. 73	2.62	4.29	10.43
Ex. 93	5.42	7.28	64.60
Ex. 97	5.83	8.64	20.32
Ex. 98	2.62	0.96	10.43

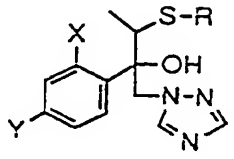
As shown above, the compounds of formula(I) and their pharmacologically acceptable salts of the present invention have a potent antifungal activity against various fungi, e.g., Candida albicans, Cryptococcus neoformans, and

Aspergillus fumigatus and, therefore, can be used for the treatment of fungal infections in mammals including human beings.

While the invention has been described in connection with the above specific embodiments, it should be recognized that various modifications and changes may be made to the present invention and also fall within the scope of the invention as defined by the claims that follow.

What is claimed is:

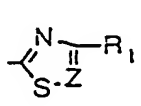
1. A triazole compound of the following formula(I) and the pharmacologically acceptable salts thereof:



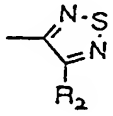
(I)

wherein:

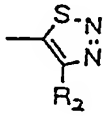
X and Y are each independently a hydrogen or halogen; and R is a group selected from the formulae consisting of (I-a), (I-b), (I-c), (I-d), (I-e), (I-f), (I-g), (I-h), (I-i) and (I-j)



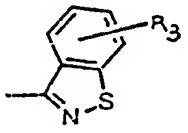
(I-a)



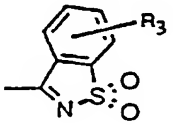
(I-b)



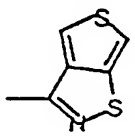
(I-c)



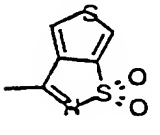
(I-d)



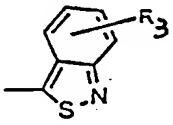
(I-e)



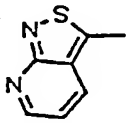
(I-f)



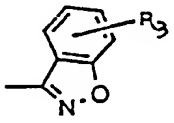
(I-g)



(I-h)



(I-i)

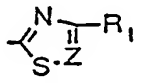


(I-j)

wherein Z is a nitrogen or carbon; R^1 represents a C_{1-4} alkoxy, C_{1-4} alkoxymethyl, C_{1-4} alkylthio, C_{1-4} alkylthiomethyl, amino, C_{1-4} alkylamino group which may form a ring with a nitrogen atom, or an optionally substituted C_{1-4} alkyl, styryl, phenyl or heteroaryl group; R^2 represents a hydrogen or C_{1-3} alkyl, phenyl, substituted phenyl, morpholinyl, pyrolidinyl, thiomorpholinyl or piperidinyl

group; and R^3 represents a hydrogen or halogen or a C_{1-3} alkyl, C_{1-3} alkoxy or nitro group.

2. The compound of claim 1 wherein R is a group of the following formula (I-a):



(I-a)

wherein R_1 is the same as defined in claim 1.

3. The compound of claim 2 which is selected from the group consisting of:

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-(3-t-butyl-1,2,4-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-(3-methylthio-1,2,4-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-(3-cyclopropyl-1,2,4-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-(3-isopropyl-1,2,4-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-(3-methoxy-1,2,4-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-(3-chloromethyl-1,2,4-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-(3-dimethylamino-1,2,4-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(pyrrolidin-1-yl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-(3-amino-1,2,4-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-(3-ethoxy-1,2,4-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-(3-methacryl-1,2,4-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-(3-methylthiomethyl-1,2,4-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-(3-ethyl-1,2,4-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(1-chloroethyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-(3-methoxymethyl-1,2,4-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(4-methoxystyryl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*,3R*)-2-(2,4-difluorophenyl)-3-[3-(3,5-dimethylpyrazol-1-yl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-(3-crotyl-1,2,4-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(4-fluorostyryl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(4-(2,2,3,3-

tetrafluoropropoxy)styryl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-(3-fluoromethyl-1,2,4-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-(3-phenoxymethyl-1,2,4-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(2-fluorophenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*,3R*)-2-(2,4-difluorophenyl)-3-[3-(2,6-difluorophenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(4-fluorophenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(2-pyridyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(2-chlorophenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-(3-phenyl-1,2,4-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(3-pyridyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(4-pyridyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-[4-(1-(N-

hydroxyiminoethyl)phenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(4-chlorophenyl)-3-[3-(3,5-difluorophenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-dichlorophenyl)-3-[3-(4-pyridyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(4-chlorophenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(3-fluorophenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*,3R*)-2-(2,4-difluorophenyl)-3-[3-(3,4-difluorophenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*,3R*)-2-(2,4-difluorophenyl)-3-[3-(2,6-dichlorophenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(3-trifluoromethylphenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(3-chlorophenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(4-(1H-imidazol-1-yl)phenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(2-pyrazinyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(2-chloro-6-fluorophenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(4-bromophenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*,3R*)-2-(2,4-difluorophenyl)-3-[3-(4-(1H-1,2,4-triazol-1-yl)phenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(4-azidophenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(3,5-bistrifluoromethylphenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-(3-styryl-1,2,4-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(4-morpholin-1-yl)phenyl-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*,3R*)-2-(2,4-difluorophenyl)-3-[3-(3-trifluoromethyl-4-acetylamino)phenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(4-(1,3,4-oxadiazol-2-yl)phenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(4-(1,3-dioxolan-2-yl)phenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-

yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(4-cyanophenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(thiophen-2-yl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(4-nitrophenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(pyrimidin-5-yl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(4-biphenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(4-(2,2,3,3-tetrafluoropropoxy)phenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(4-(4-pyridon-1-yl)phenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*,3R*)-2-(2,4-difluorophenyl)-3-[3-(4-methylpyrimidin-2-yl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*,3R*)-2-(2,4-difluorophenyl)-3-[3-(pyridin-N-oxo-4-yl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*,3R*)-2-(2,4-difluorophenyl)-3-[3-(4-methylthiophenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(4-methanesulfonylphenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(3-nitrophenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*,3R*)-2-(2,4-difluorophenyl)-3-[3-(2,5-difluorophenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(4-dimethylaminophenyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(1H-1,2,4-triazol-1-yl)methyl-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(4-methoxystyryl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(3-pyrrol-1-yl)phenyl-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(pyridazin-3-yl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(1-chloro-2-methoxyethyl)-1,2,4-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-(3-methoxymethyl-1,2,4-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R, 3R)-2-(2,4-difluorophenyl)-3-(3-styryl-1,2,4-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R, 3R)-2-(2,4-difluorophenyl)-3-(3-methoxy-1,2,4-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*,3R*)-2-(4-chlorophenyl)-3-(3-methoxy-1,2,4-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*,3R*)-2-(4-fluorophenyl)-3-(3-methoxy-1,2,4-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(4-fluorophenyl)-3-(3-styryl-1,2,4-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*,3R*)-2-(2,4-difluorophenyl)-3-[4-(2,6-difluorophenyl)-thiazol-2-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*,3R*)-2-(2,4-difluorophenyl)-3-[4-(2,4-dichlorophenyl)-thiazol-2-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-[4-(4-chlorophenyl)-thiazol-2-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-(4-ethylthiazol-2-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-[4-(1-hydroxy-1-methylethyl)-thiazol-2-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

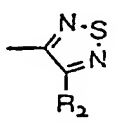
(2R*, 3R*)-2-(2,4-difluorophenyl)-3-(4-styrylthiazol-2-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-[4-(4-methoxystyryl)-thiazol-2-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol; and

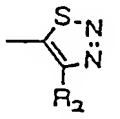
(2R*,3R*)-2-(2,4-difluorophenyl)-3-[4-(2,3-dichlorostyryl)-

thiazol-2-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol.

4. The compound of claim 1 wherein R is a group of formula (I-b) or (I-c):



(I-b)



(I-c)

wherein R_2 is the same as defined in claim 1.

5. The compound of claim 4 which is selected from the group consisting of:

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-(1,2,3-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*,3R*)-2-(4-chlorophenyl)-3-(1,2,3-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-dichlorophenyl)-3-(1,2,3-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-(4-methyl-1,2,3-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-(4-phenyl-1,2,3-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*,3R*)-2-(2,4-difluorophenyl)-3-[4-(2,4-difluorophenyl)-1,2,3-thiadiazol-5-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*,3R*)-2-(4-fluorophenyl)-3-(1,2,3-thiadiazol-5-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(N-morpholinyl)-1,2,5-thiadiazol-4-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

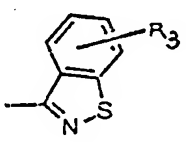
(2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(N-thiomorpholinyl)-1,2,5-thiadiazol-4-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(piperidin-1-yl)-1,2,5-thiadiazol-4-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

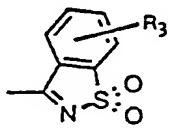
(2R*, 3R*)-2-(2,4-difluorophenyl)-3-[3-(pyrrolidin-1-yl)-1,2,5-thiadiazol-4-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol; and

(2R, 3R)-2-(2,4-difluorophenyl)-3-[3-(N-thiomorpholinyl)-1,2,5-thiadiazol-4-yl]thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol.

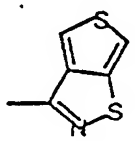
6. The compound of claim 1 wherein R is a group selected from the formulae consisting of (I-d), (I-e), (I-f), (I-g), (I-h), (I-i) and (I-j):



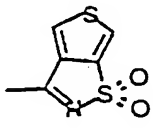
(I-d)



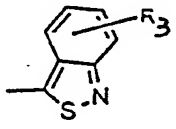
(I-e)



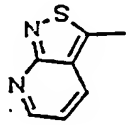
(I-f)



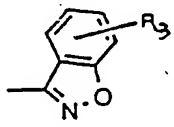
(I-g)



(I-h)



(I-i)



(I-j)

wherein R_3 is the same as defined in claim 1.

7. The compound of claim 6 which is selected from the group consisting of:

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-(1,2-benzoisothiazol-3-yl) thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R, 3R)-2-(2,4-difluorophenyl)-3-(1,2-benzoisothiazol-3-yl) thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(4-chlorophenyl)-3-(1,2-benzoisothiazol-3-yl) thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(4-fluorophenyl)-3-(1,2-benzoisothiazol-3-yl) thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-(5-chloro-1,2-benzoisothiazol-3-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(4-chlorophenyl)-3-(5-chloro-1,2-benzoisothiazol-3-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-(5,6-dimethoxy-1,2-benzoisothiazol-3-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-(5-methyl-1,2-benzoisothiazol-3-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-(7-chloro-1,2-benzoisothiazol-3-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-(thieno[3,4-d]isothiazol-3-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-(1,2-benzoisothiazol-1,1-dioxo-3-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-(thieno[3,4-d]isothiazol-1,1-dioxo-3-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-(2,1-benzoisothiazol-3-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

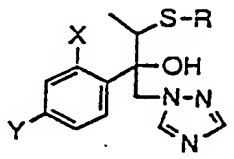
(2R*, 3R*)-2-(2,4-difluorophenyl)-3-(5-nitro-2,1-benzoisothiazol-3-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

(2R*, 3R*)-2-(2,4-difluorophenyl)-3-(isothiazolo[3,4-b]pyridin-3-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol;

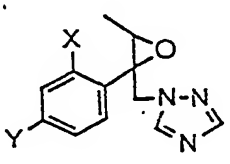
(2R*, 3R*)-2-(2,4-difluorophenyl)-3-(1,2-benzoisothiazol-3-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol oxalate; and

(2R,3R)-2-(2,4-difluorophenyl)-3-(thieno[3,4-d]isothiazol-3-yl)thio-1-(1H-1,2,4-triazol-1-yl)-2-butanol.

8. A process for preparing a triazole compound of formula (I) comprising reacting a compound of formula (II) with a compound of formula (III) or its alkali metal salt in the presence of lithium perchlorate:



(I)



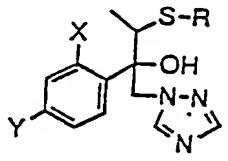
(II)

HS - R (III)

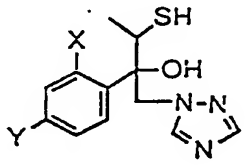
wherein:

X, Y and R are the same as defined in claim 1.

9. A process for preparing a triazole compound of formula (I) comprising reacting a compound of formula (IV) with a compound of formula (V) in the presence of a base:



(I)



(IV)

L - R (V)

wherein:
X, Y and R are the same as defined in claim 1;
L is a halogen.

10. A pharmaceutical composition comprising a therapertically effective amount of the triazole compound defined in claim 1 as an active ingredient, and a pharmaceutically acceptable carrier or adjuvant.

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/KR 95/00019

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/KR 95/00019

A. CLASSIFICATION OF SUBJECT MATTER

IPC[6] : C 07 D 417/12, 413/12; A 61 K 31/41

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC[6] : C 07 D 417/00, 413/00, 251/00; A 61 K 31/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

AT, Chem. Abstr.

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Questel: DARC, CAS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	EP 0 091 309 A2 (PFIZER) 12 October 1983 (12.10.83), claim 1, examples 5,9,10,24.	1
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☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
02 May 1995 (02.05.95)	11 May 1995 (11.05.95)

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